FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE (REV. 1094) TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		ATTORNEY'S DOCKET NUMBER H0535/7013 U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 10/031833
INTERNATIONAL APPLICATION NO. PCT/US00/20210	INTERNATIONAL FILING DATE 24 July 2000 (24.07.00)	PRIORITY DATE CLAIMED 22 July 1999 (22.07.99)
TITLE OF INVENTION LINKAGE OF AGENTS TO TISSUE		
APPLICANT(S) FOR DO/EO/US GREEN, Howard, RANDO, Robert R.		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371©(4)).

10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(C)(5)).

Items 11. To 16. Below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98 with references.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.

14. ☐ A SECOND or SUBSEQUENT preliminary amendment.

15. ☐ A substitute specification.

16. ☐ A change of power of attorney and/or address letter.

17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C.1.821-1.825.

18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).

19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).

20. ☒ Other items or information:
    Copy of page 1 of PCT Published Application

Express Mail Label No. EL840386315US (IFD/ERG)
Mailed January 22, 2002

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5)	INTERNATIONAL APPLICATION	ATTORNEY'S DOCKET NUMBER
10/031833	PCT/US00/20210	H0535/7013

21. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):		CALCULATIONS PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1000.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$860.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but but international search fee paid to USPTO (37 CFR 1.445(a)(2)).paid to USPTO	$710.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) But all claims did not satisfy provisions of PCT Article 33(1)-(4)	$690.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =		$ 690.00

Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 X 30 Months from the earliest claimed priority date (37 CFR 1.492(e)).				$ 130.00	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	20- 20 =	0	X $18.00	$ 0.00	
Independent Claims	9 - 3 =	6	X $80.00	$ 480.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+$270.00	$ 0.00	
TOTAL OF ABOVE CALCULATIONS =				$ 1300.00	
☒ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above Are reduced by ½.				$ 650.00	
SUBTOTAL =				$ 650.00	
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐30 Months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$ 650.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate coversheet (37 CFR 3.28, 3.31). $40.00 per property +				$	
TOTAL FEES ENCLOSED =				$ 650.00	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of $ 650.00 to cover the above fees is enclosed.

b. ☐ Please charge by Deposit Account No. _____ In the amount of $_____ To cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23/2825. A duplicate of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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10/031833

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

531 Rec'd PCT/PTO 22 JAN 2002

International Application No.	:	PCT/US00/20210
International Filing Date	:	24 July 2000 (24.07.00)
Earliest Priority Date	:	22 July 1999 (22.07.99)
Applicant(s)	:	PERICOR SCIENCE, INC. ET AL.
Title	:	LINKAGE OF AGENTS TO TISSUE

Commissioner for Patents
Washington, DC 20231

PRELIMINARY AMENDMENT

Sir:

In the Claims

Please cancel claims 14-16, 18, 19, 21, 24-33, 35-44, 46-58 and 60-73, prior to calculating fees, and without prejudice to future prosecution.

Remarks

Claims 14-16, 18, 19, 21, 24-33, 35-44, 46-58 and 60-73 are cancelled without prejudice to future prosecution. Claims 1-13, 17, 20, 22, 23, 34, 45 and 59 are now pending.

Respectfully submitted,

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Attorney Docket No.: H0535/7010WO
Date: January 22, 2002
X01/22/02

LINKAGE OF AGENTS TO TISSUE

Field of the Invention

This invention relates to the linkage of agents to tissue by certain reactive moieties and involves methods, products and kits relating thereto.

Background of the Invention

Transglutaminases are a family of calcium-dependent enzymes mediating covalent cross-linking reactions between specific peptide bound (-glutamyl residues and various primary amino groups of peptide-bound lysines or polyamines, acting as amine donor substrates (Davies, et al., *Adv. Exp. Med. Biol.* 250, 391-401, 1988). These enzymes stabilize biological structures via the formation of isopeptide cross-links. In mammals, at least five enzymatically active transglutaminases have been identified, cloned and sequenced. The number of proteins acting as glutaminyl substrates for transglutaminases is restricted, and no obvious consensus sequence around these substrates' glutamines has been found.

More recently, people in the art determined that as long as polypeptides including stretches of polyglutamine are rendered sufficiently soluble by the flanking residues, all were excellent substrates of transglutaminase. It also is described in U.S. Patent 5,525,336 (the disclosure of which is incorporated herein by reference in its entirety) that transglutaminases and corneocyte proteins, the natural substrates of transglutaminases, can be used together as cosmetic treatments to cross-link preparations of corneocyte proteins to the outer layer of skin, hair or nails to form a protective layer on the skin, hair or nails. U.S. Patent 5,490,980 describes selecting agents having or modifying agents to have an aliphatic amine, and then attaching those agents to skin, hair or nails using transglutaminase. While the idea was sound in principle, in practice the '980 applicants achieved results that were barely above background. (See Example Section of '980 patent). An aliphatic amine was applied in the examples as a single linking molecule or prophetically in clusters (according to a formula in the '980 patent).

Summary of the Invention

It has been discovered, surprisingly, that certain compounds are particularly desirable for use as reactive molecules to attach agents to proteinaceous material such as body tissue. Methods of attaching agents to body tissue and methods of screening molecules using compounds with certain reactive moieties are provided. In addition, compositions of matter

suitable as reactive molecules for attachment to agents, and kits containing such molecules and/or conjugates are provided.

In one aspect of the invention a composition of matter is provided comprising a compound having a structure of Formula I

Formula I

X_2 -- L_2 -- A -- L_1 -- X_1

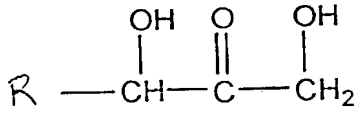
wherein A is an agent; L_1 and L_2 are independently selected organic linkers (i.e., linking molecules) or bonds; X_1 and X_2 are reactive moieties independently selected from Group A reactive moieties, and, in some instances, N-hydroxyl succinimide or N-alkyl maleimide, and wherein L_2 and X_2 may be present or absent, however if L_2 is absent, then X_2 is also absent. Compounds of Formula I can be both monofunctional, provided X_1 or X_2, but not both are present, or if both are present, the compound is bifunctional.

In important embodiments, the agent is provided in a microparticle. In other embodiments, the reactive moiety is not native to the agent. In important embodiments, the reactive moieties are dihydroxyacetone.

Preferred monofunctional reactive moieties which can be linked to the agent are as described herein. The monofunctional reactive moieties of Group A are most particularly suited for linkage to non-protein or non-peptide based agents. Since many of these reactive moieties react with amines (such as those present in lysines) or thiols (such as those present in cysteines), it is recommended that the agent to which they attach possesses neither amines nor thiols. This will prevent the reactive moieties from reacting with the agent rather than the intended body tissue.

Some preferred monofunctional reactive moieties are shown below in Group A. The R group may be any organic or inorganic molecule. In some instances, R may include the agent or a microparticle comprising the agent.

Group A Reactive Moieties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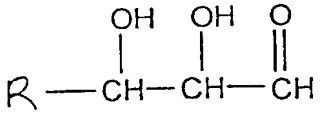
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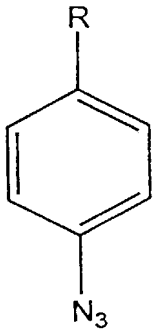
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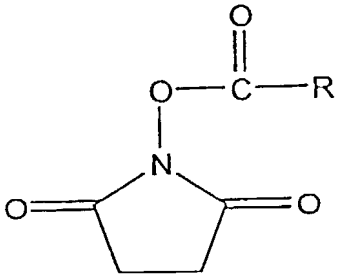
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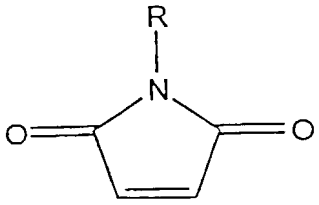
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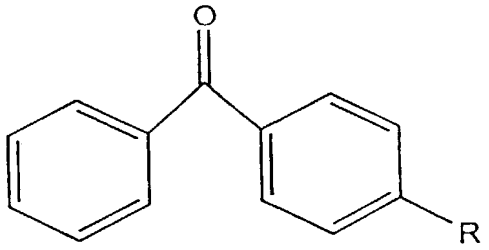
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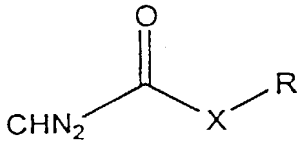
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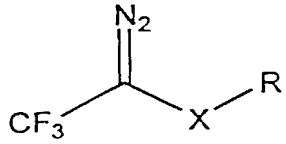
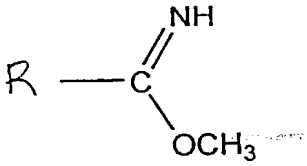

(H)

X = N, O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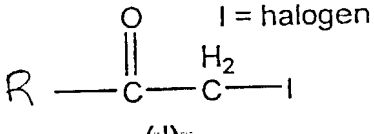
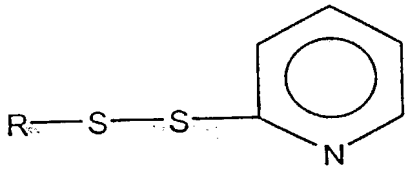
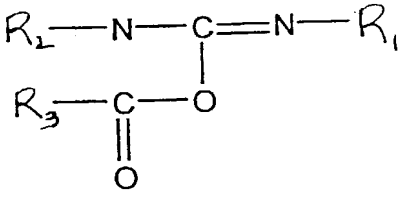

(J)

I = halogen


(K)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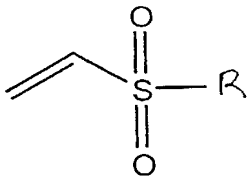
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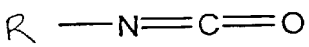

(N)

Group A also includes derivatives of the foregoing molecules described in greater detail below and known to those or ordinary skill in the art in view of the teachings herein.

As used herein, in some embodiments, the agent, A, is selected from the group consisting of a sunscreen agent, a cosmetic, an enzyme, a coloring agent, a pharmaceutical agent, a member of a ligand/receptor pair, a tissue sealant, a wound healing agent, a bulking agent, a hair conditioning agent, a hair fixative, an anti-foaming agent, a moisturizing agent, a humectant, a depilatory agent, an anti-nerve gas agent including an enzyme that degrades nerve agents, an anti-neurotoxin, a film forming agent, a vitamin, an insect repellant and a component of a high affinity noncovalent coupling (e.g., biotin or avidin). Preferably, if the reactive moieties of Group A are used, then A is not a protein or a peptide or does not contain amine or thiol groups (as are present in lysine and cysteine, respectively). In some embodiments, A is not an anti-nerve gas agent.

In one embodiment, the agent is selected from the group consisting of cholinesterase and phosphodiesterase. In another embodiment, the agent is an enzyme that degrades nerve agents, such as organophosphate agents. In a preferred embodiment, the agent is selected from the group consisting of OPAA anhydrolase (prolidase) and squid type OPA anhydrase. In another embodiment, the agent is a nonprotein. In one embodiment, the agent is not itself able to conjugate directly to proteinaceous material or conjugates only weakly. Thus, the agent is conjugated to a reactive moiety whereby the agent may be attached to the body tissue via the covalent bond resulting between the reactive moiety and the proteinaceous material. As used herein, a proteinaceous material is minimally defined as a material that contains thiols and/or amines and to which the reactive moieties of the invention may covalently attach in a spontaneous manner. The preferred proteinaceous material is body tissue, including the integument, a wound bed, internal organs or internal tissue of a living subject. In yet another embodiment, the agent in its native form (e.g., free of conjugation to either the linker (i.e., linking molecule) or the reactive moiety) is not able to covalently attach to a body tissue spontaneously. In a related embodiment, the linker (when not conjugated to the reactive moiety) is not able to covalently attach to a body tissue spontaneously.

In important embodiments, the reactive moiety is dihydroxyacetone. Thus, X_1, X_2 or both X_1 and X_2 may be dihydroxyacetone, according to some embodiments.

In another aspect, the invention provides a method for attaching an agent to a body tissue comprising applying to the body tissue a compound having a structure of Formula I in

an effective amount, and allowing crosslinking to occur. In preferred embodiments, the conjugate of agent, linker and reactive moiety (i.e., the compound of Formula I) is formed prior to application to the body tissue. Depending on the reactive group, crosslinking may occur with no additional physical requirements or with additional physical requirements such as light, heat, catalysts, etc. As used herein, a body tissue can be an integument, skin, hair and nails, a wound bed, or an internal body tissue. The compound of Formula I to be used in this method may incorporate a cosmetic agent, a bulking agent, a hair conditioning agent, a hair fixative, a sunscreen agent, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, an insect repellant, a coloring agent, a pharmaceutical agent, a ligand-receptor complex or a receptor of a ligand-receptor complex, although agents which do not possess amine or thiol groups are generally preferred when using the monofunctional reactive moieties of Group A. Thus, the invention may be used for a number of different purposes depending upon the nature of the particular agent used in the compositions and methods.

In some embodiments, the agents, the linkers or the agent-linker conjugates may be provided in the form of a microparticle. In yet other embodiments, the agents, the linkers or the agent-linker conjugates do not comprise a microparticle.

In one aspect, the invention therefore also provides a method for coloring hair by applying to hair a compound of Formula I, wherein the agent is a coloring agent such as those described herein, in an effective amount to change the color of untreated hair.

In another aspect, the invention provides a method for moisturizing skin by applying to the skin a compound having a structure of Formula I, wherein the agent is a moisturizing agent as described herein, in an effective amount to improve hydration of skin.

In another aspect, the invention provides methods for bulking hair, for conditioning hair, for attaching a sunscreen agent, for topically applying a pharmaceutical, etc.

In one embodiment, the tissue can be pretreated to make it more receptive to crosslinking with the reactive moiety. In one embodiment described above, this is accomplished by attaching polymers rich in reactive molecules such as glutamine, lysine or both glutamine and lysine to the body tissue. In other embodiments, the tissue is treated to expose reactive molecules by washing, chemical treatment, etc. Detergents and lipases can be used to remove fatty acids and oils. Roughening agents such as pumice, silica and sandpaper can be employed to remove dead tissue and other obstructions, and chemical agents

such as sodium hydroxide can be used to expose reactive molecules. Combinations of the foregoing are contemplated.

As suggested from Formula I compounds, the invention provides monofunctional reactive compounds (e.g., where either X_1 or X_2 is absent) or bifunctional reactive compounds (e.g., where both X_1 and X_2 are present). The invention further provides compositions and methods of use of other bifunctional reactive compounds which do not comprise an agent. These bifunctional reactive compounds have the structure of Formula II:

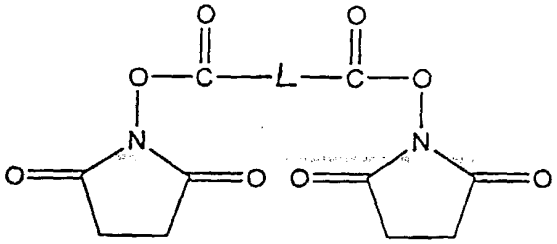
Formula II

$$X_2 -- L -- X_1$$

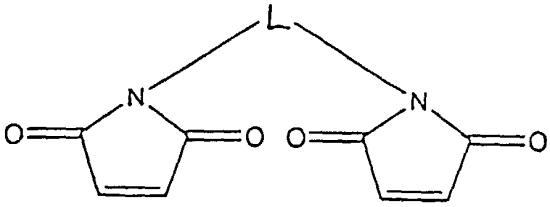
wherein L is an organic linker or bond; and X_1 and X_2 are reactive moieties independently selected from the reactive moieties of Group A, N-hydroxy-succinimide and N-alkyl-maleimide and derivatives thereof, as well as any other reactive moiety described herein.

Compounds of Formula II embrace the structures of bis-N-hydroxy-succinimide or bis-N-alkyl maleimide shown below.

Examples of Formula II Compounds



bis-N-hydroxy-succinimide



bis-N-alkyl-maleimide

Bifunctional reactive molecules can be used to link a tissue to an agent, or to link a tissue to a microparticle, or to link a microparticle to an agent, or to link to two tissues together, but is not so limited. Some bifunctional reactive molecules can also deliver an agent. This latter group of molecules include compounds of Formula I where both X_1 and X_2 are present and compounds of Formula III where both X_1, X_2, and any of A_1, A_2 or A_3 are present.

In another aspect, the invention provides a method for sealing tissue comprising applying a force to hold two tissues in contact with each other in the presence of an effective amount of a compound of Formula II to crosslink the two tissues, and allowing crosslinking to occur. In important embodiments, these latter compounds are used to glue tissues together. The tissue may be held together during the crosslinking process by any conventional means, such as sutures, tape, stapes and the like. Formula I compounds in which L_1, X_1, L_2, and X_2 are all present can also be used to link two tissues together in a similar manner as Formula II compounds. This latter category of Formula I compounds are also able to provide the two tissues with an agent while sealing them together. Similarly, derivatives of Formula II compounds which are linked to an agent (as described below) can also seal two tissues and provide them with an agent.

Thus, in related aspects, the invention provides compositions, methods and kits that include compounds that are derivatives of Formula II and which have the structure of Formula III:

Formula III

$$A_2 -- X_2 -- L -- X_1 -- A_1$$
$$|$$
$$A_3$$

wherein A1, A2, and A3 are agents, L is an organic linker and X_1 and X_2 are reactive moieties independently selected from Group A, N-hydroxy-succinimide, N-alkyl maleimide, and derivatives thereof; wherein either A_1 or A_2 may be present, but not both, and wherein A_3 is present independently of the presence of A_1 or A_2. Any or all of A_1, A_2 and A_3 may be a microparticle. In some embodiments: A_1 is absent; A_2 is absent; A_3 is absent; A_1 and A_3 are

absent; A_1 and A_2 are absent; A_2 and A_3 are absent; or A_1, A_2 and A_3 are absent, thereby reverting the Formula III compound to a Formula II compound.

In another aspect, the invention provides a method for attaching an agent to a body tissue comprising applying to the body tissue a compound having a structure of Formula II in an effective amount, applying to the body tissue an agent, and allowing crosslinking to occur. The agent may be applied to the body tissue prior to, simultaneously with, or following the application of the Formula II compound.

Depending on the reactive moiety used, crosslinking may occur with no additional physical requirements or with additional physical requirements such as application of light, heat, catalysts, etc. As used herein, a body tissue can be an integument, skin, hair and nails, a wound bed, or an internal body tissue. The compounds of Formula II (including the subset described above) to be used in this method may incorporate a cosmetic agent, a bulking agent, a hair conditioning agent, a hair fixative, a sunscreen agent, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, an insect repellant, a coloring agent, a pharmaceutical agent, a ligand-receptor complex or a receptor of a ligand-receptor complex. The bifunctional reactive molecules (e.g., compounds of Formula II) are most preferably suited to agents which are proteins or peptides particularly when compared to monofunctional reactive compounds of Formula I (i.e., where X_1 is present or X_2 is present, but not both). These bifunctional compounds can be used with agents which possess amines (such as are present in lysine) or thiols (such as are present in cysteines).

In one aspect, the invention therefore also provides a method for coloring hair by applying to hair a compound of Formula II, wherein the agent is a coloring agent such as those described herein, in an effective amount to change the color of untreated hair.

In another aspect, the invention provides a method for moisturizing skin by applying to the skin a compound having a structure of Formula II, wherein the agent is a moisturizing agent as described herein, in an effective amount to improve hydration of skin.

In another aspect, the invention provides methods for bulking hair, for conditioning hair, for attaching a sunscreen agent, for topically applying a pharmaceutical, etc.

The invention, in another aspect, provides a pharmaceutical composition comprising an effective amount of a compound of Formula I where A is a pharmaceutical agent, and a pharmaceutically acceptable carrier. In a related aspect, the invention provides a pharmaceutical composition comprising an effective amount of a compound of Formula II

(which may optionally comprise an agent) and a pharmaceutically acceptable carrier. The invention, in another aspect, provides cosmetic compositions, skin protective compositions, nerve-gas deactivating compositions, etc. which may comprise a compound in which the agent is a cosmetic agent, a bulking agent, a hair conditioning agent, a hair fixative, a sunscreen agent, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, an insect repellant, a coloring agent, a ligand-receptor complex or a receptor of a ligand-receptor complex.

In yet another aspect of the invention, a kit is provided comprising a package which houses a container containing a compound of Formula I, Formula II or Formula III and instructions for use. The container also can contain catalysts, microparticles, cleansers, vehicles, preservatives and buffers. In preferred embodiments, the compounds of Formula I comprise dihydroxyacetone as the reactive moiety.

In yet another aspect, a method is provided of treating a subject to attach microparticles to a skin surface of the subject comprising contacting the skin surface with microparticles having surface available reactive moieties in an amount sufficient to attach the microparticles to the skin surface, and allowing the microparticles to remain in contact with the skin surface for a time sufficient to permit a layer of microparticles to covalently attach to the skin surface. The surface available reactive moieties are selected from the group consisting of reactive moieties of Group A, N-hydroxy-succinimide and N-alkyl-maleimide, derivatives thereof, other reactive moieties mentioned herein. In one embodiment, the layer of microparticles is non-planar. In another embodiment, the microparticles further comprise an agent, or an active agent, or a non-nucleic acid active agent, or a non-protein active agent.

The agent may be, but need not be, selected from the group consisting of a cosmetic agent, a bulking agent, a hair conditioning agent, a hair fixative, a sunscreen agent, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, an insect repellant, a coloring agent, a pharmaceutical agent, a ligand-receptor complex and a receptor of a ligand-receptor complex. In some embodiments, the agent does not itself contain a reactive moiety.

In one embodiment, the microparticles further comprise a synthetic polymer, and in preferred embodiments, the synthetic polymer is latex or polystyrene. In other embodiments, the microparticles are non-biodegradable, water insoluble and/or detergent insoluble.

The microparticles may be hollow or porous but are not so limited. In certain embodiments, the microparticles' size is selected from the group consisting of greater than 5 μm, less than 5 μm, less than 1 μm, 100 nm to 500 nm, less than 100 nm, 20 nm to 90 nm, 20 nm to 35 nm, less than 20 nm, 1 nm to 10 nm and 5 nm to 10 nm. These sizes and ranges can be cut-offs or can represent average size determinations.

In some embodiments, the microparticles enter the cornified layer of the skin but not the layer of living cells. However, in other embodiments, the agent contained within the microparticle may be able to enter the layer of living cells.

In one embodiment, the reactive moieties are part of a polymer, preferably wherein the polymer is covalently attached to the microparticle. In a related embodiment, the polymer is comprised of at least 20%, at least 30%, at least 40%, at least 50% units having reactive moieties, or is rich in units having reactive moieties at a surface available terminus, or is selected from the group of polymers consisting of: at least two contiguous linked units having reactive moieties, at least three contiguous linked units having reactive moieties, at least four contiguous linked units having reactive moieties, at least five contiguous linked units having reactive moieties, at least ten contiguous linked units having reactive moieties, at least fifteen contiguous linked units having reactive moieties, and at least twenty contiguous linked units having reactive moieties.

Any of foregoing embodiments may apply to the compositions, methods, and kits provided by the invention, including those relating to microparticles.

In another aspect, the invention provides a method of treating a subject to attach microparticles (or an agent) to a skin surface of the subject comprising contacting the skin surface with a bifunctional reactive compound of Formula I, II or III, contacting the skin with microparticles (or an agent) having surface available amines or thiols in an amount sufficient to attach the microparticles (or an agent) to the skin surface in the presence of the bifunctional reactive compound of Formula I, II or III, and allowing the microparticles (or an agent) and compound of Formula I, II or III to remain in contact with the skin surface for a time sufficient to permit a layer of microparticles (or an agent) to covalently attach to the skin surface.

In one embodiment, the surface available reactive amines or thiols are present as lysines or cysteines, respectively. In another embodiment, the reactive amines or thiols are part of a polymer, and the polymer may be covalently attached to the microparticle (or an

agent), or simply present in the microparticle matrix. In other embodiments, the polymer is comprised of at least 50% amines, at least 50% thiols, at least 50% lysines, or at least 50% cysteines, or the polymer is amine-rich or lysine-rich at a surface available terminus, or it is thiol-rich or cysteine-rich at a surface available terminus, or it comprises a polymer selected from the group consisting of: at least two contiguous linked amines, lysines, thiols, or cysteines, at least three contiguous linked amines, lysines, thiols, or cysteines, at least four contiguous linked amines, lysines, thiols, or cysteines, at least five contiguous linked amines, lysines, thiols, or cysteines, at least ten contiguous linked amines, lysines, thiols, or cysteines, at least fifteen contiguous linked amines, lysines, thiols, or cysteines, and at least twenty contiguous linked amines, lysines, thiols, or cysteines.

In a further aspect, the invention provides a composition comprising a microparticle comprising an active agent and a polymer rich in reactive molecules, wherein the microparticle is non-biodegradable, and the reactive molecules are surface available. In certain embodiments, the active agent is a nucleic acid agent, or a non-nucleic acid active agent, or a protein agent, or a non-protein active agent, or the active agent is selected from the group consisting of a cosmetic agent, a bulking agent, a hair conditioning agent, a hair fixative, a sunscreen agent, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, an insect repellant, a coloring agent, a pharmaceutical agent, a ligand-receptor complex and a receptor of a ligand-receptor complex. In some preferred embodiments, the active agent does not itself contain a reactive molecule. In other embodiments, the microparticle further comprises a synthetic polymer and preferably the synthetic polymer is latex or polystyrene. In some embodiments, the polymer rich in reactive molecules is covalently linked to the synthetic polymer. In other embodiments, the microparticles' size is selected from the group consisting of greater than 5 μm, less than 5 μm, less than 1 μm, 100 nm to 500 nm, less than 100 nm, 20 nm to 90 nm, 20 nm to 35 nm, less than 20 nm, 1 nm to 10 nm and 5 nm to 10 nm. In some embodiment, the microparticle is non-biodegradable, water insoluble and/or or detergent insoluble.

In another embodiment, the reactive molecules are surface available in an amount sufficient to attach the microparticle to a skin surface in the presence of a compound of Formula I, II and III. In certain embodiments, the polymer comprises units and at least 50% of units have reactive moieties, or the polymer is rich in reactive moieties at a surface available terminus, or the polymer is covalently attached to the microparticle, or the polymer

comprises units having reactive moieties wherein the polymer is selected from the group consisting of at least two contiguous linked units having reactive moieties, at least three contiguous linked units having reactive moieties, at least four contiguous linked units having reactive moieties, and at least five contiguous linked units having reactive moieties.

In yet a further aspect, the invention provides a composition comprising a microparticle comprising a non-nucleic acid active agent, and covalently attached surface available reactive molecules, wherein the microparticle is 100 nm to 500 nm in size. Other sizes are as described above. In one embodiment, the surface available reactive moieties are present as free pendant groups.

In yet another aspect, the invention provides a kit comprising any of the microparticles of the invention. In one aspect, the kit includes a microparticle comprising surface available reactive moieties in an amount sufficient to attach the microparticle to a skin surface, and instructions for topically administering the microparticle to a skin surface, wherein the surface available reactive moieties are selected from the group consisting of reactive moieties of Group A, N-hydroxyl-succinimide, and N-alkyl-maleimide, and derivatives thereof, and the like. The kit may further comprise a polylysine polymer for attachment to the skin surface, in one embodiment. In another embodiment, the kit may further comprise a cleanser.

In one embodiment, the microparticle is provided in a topically administered form selected from the group consisting of an ointment, an aerosol, a gel, and a lotion. In another embodiment, the kit further comprises an agent in a separate container.

In another aspect, a kit is provided comprising a bifunctional reactive molecule in an amount sufficient to crosslink a skin surface, and a microparticle comprising surface available reactive moieties in an amount sufficient to attach the microparticle to the bifunctional reactive molecule, wherein the surface available reactive moieties are selected from the group consisting of amines and thiols. In one embodiment, the kit further comprises instructions for topically administering the bifunctional reactive molecule and the microparticle to a skin surface. In another embodiment, the kit further comprises a cleanser.

In any of the foregoing embodiments, reactive moieties that are photoreactive, as described in greater detail below, may also be used in the compounds of Formula I, II and III. In such embodiments, attachment of such reactive moieties to body tissues, for example, require the application of light of a particular wavelength, as will be described herein.

These and other aspects of the invention are described in further detail below.

Brief Description of the Drawing

Figure 1 is a schematic of a kit of the invention.

Detailed Description

The invention is based in part on the discovery that compounds bearing reactive carbonyl and hydroxyl groups are particularly useful for attaching agents to proteinaceous material such as body tissues, including external surfaces such as skin, hair, and nails. One category of such agent-bearing compounds have the structure of Formula I:

Formula I

$$X_2 -- L_2 -- A -- L_1 -- X_1$$

where A is an agent; L_1 and L_2 are independently organic linkers or bonds; X_1 and X_2 are reactive moieties independently selected from Group A, N-hydroxyl succinimide or N-alkyl maleimide, derivatives thereof, as well as any of the other reactive molecules described herein; L_2 and X_2 may be present or absent, however if L_2 is absent, then X_2 is also absent. The agent may be provided in the form of a microparticle.

As used herein, the term "reactive moiety" refers to the reactive chemical group or structure which reacts with its counterpart to form crosslinks. Examples of reactive moieties useful in the invention include the reactive carbonyl groups and Michael acceptors of Group A. A reactive molecule comprises one or more reactive moieties. Compounds of Formula I, Formula II, and Formula II are all reactive molecules.

Group A reactive moieties contain reactive moieties which covalently attach to proteinaceous materials. Proteinaceous materials, as used herein, refer to materials which possess at least thiol and/or amine groups, and preferably comprise amino acids or peptides containing thiol and/or amine groups. Some Group A compounds, such as compounds (A), (B), (C) and (F), possess a reactive carbonyl group, while others, such as compounds (D) and (M) possess reactive Michael acceptors. In general, reactive carbonyl groups attack amine groups such as those present in lysine residues. As an example, 1,2-dihydroxyacetone undergoes oxidative transformations in situ to generate cross-links with endogenous amines, including the ε-amino group of lysine. Reactive Michael acceptors, on the other hand, are thiol reactive, and thus preferentially target cysteine residues. Other suitable reactive compounds useful in the invention include imidoesters, active halogen compounds, EDC

coupled compounds, pyridyl disulfide compounds, vinyl-sulfone containing compounds, and isocyanate containing compounds.

One of ordinary skill in the art would appreciate that in addition to the moieties presented in Group A, derivatives of these moieties are also useful and thus embraced by the invention. Other examples of reactive moieties which can be used in the compositions and methods of the invention include: AMINOETHYL-8 REAGENT®, 2-aminoethyl-2'-aminoethanethiolsulfonate, BMPA, TCEP-HCl, BNPS-skatole, citraconic anydride, DCC, DTPA, EMCA, N-ethylmaleimide, HPG, iodoacetic acid, KMUA, mono(lactosylamido) mono(succinimidyl) suberate, MSA, PMSF, sulfo-N-hydroxy-succinimide, SATA, SATP, SBF-chloride, SPB, sulfo-N-hydroxyl-succinimide acetate, sulfo-SHB, sulfo-SDTB, TFCS, Traut's Reagent, water-soluble Bolton Hunter Reagent, HPPH and β-(4-hydroxyphenyl)ethylmaleimide. All of these compounds are commercially available from Pierce Chemical Company.

Yet another category of reactive moieties useful in compounds of the invention is photoreactive modifying moieties. Photoreactive moieties are able to modify epidermal proteins as a consequence of light activation. Although chemically unreactive in the absence of light, these reagents become transiently reactive upon illumination by wavelengths of light within their absorption spectrum. Suitable wavelengths are typically in the 300-500 nm range. These reagents are generally highly photosensitive and, consequently, are readily photoactivated.

Thus, according to one embodiment of the present invention, the reactive moiety is a photoreactive moiety which is linked to an agent either directly or indirectly through the use of a linker. The resultant reactive molecule can be applied to the epidermis (i.e., skin), nails or hair, followed by limited exposure to an appropriate wavelength. Light damage to the skin is probably unlikely given the enormous photosensitivity of these molecules.

Photoreactive modifying reactive moieties are well known to those of ordinary skill in the art. Examples of such compounds include phenyl azides, benzophenones, diazo esters/amides and trifluoromethyl diazo esters/amides. Due to the high reactivity of these compounds, they are able to covalently attach to a variety of groups, including but not limited to amines and thiols. Upon appropriate light exposure, phenyl azides release a N_2 and present a free nitrogen radical (see Group A, compound E). Benzophenones on the other hand, convert their carbonyl group to a free radical (see Group A, compound F). Diazo

esters/amides (Group A, compound G) and trifluomethyl diazo esters/amides (Group A, compound H) both form diradical carbons by releasing N_2 following exposure to light.

The site of action for the compounds of the invention will depend on the extent to which these compounds can penetrate the surfaces or tissues to which they are applied. As an example, the action of an agent conjugated to the skin via dihydroxyacetone is generally limited to the upper layers of the skin. Again depending upon the reactive moiety used, the reaction time and conditions necessary to effect a covalent attachment will differ. Dihydroxyacetone interaction with skin generally requires about 2 hours for optimal covalent attachment. However, conditions may be varied so as to reduce this reaction time. Such variables are well known to one of ordinary skill in the art.

It is to be understood that any of the reactive moieties discussed herein, including derivatives thereof, may be incorporated into the compounds of Formula I, II and III, as appropriate. Thus, although some examples provided herein may focus on reactive groups which are useful in Formula I or II or III, these moieties may be suitable in all three of these formulae.

In general, the agents are chemical agents and include, but are not limited to, pharmaceutical agents, enzymes, cosmetics, bulking agents, hair conditioner agents, hair fixative agents, anti-foaming agents, antistatic agents, moisturizing agents including humectants, depilatories (i.e., hair removal agents), vitamins, film forming agents such as those used in hair fixatives or wound healing, anti-nerve gas or anti-neurotoxin agents, sunscreen agents, ligands of ligand-receptor pairs, receptors of ligand-receptor pairs, components of high affinity noncovalent bonding pairs, insecticides and repellants including louse repellents, bactericides, fungicides, tissue sealants, labels, structural proteins, chelating agents, microparticles and the like. Anti-nerve gas agents include enzymes which degrade nerve agents (e.g., organophosphate nerve agents). Examples include OPAA anhydrolase (prolidase) and the squid type OPA anhydrase. Other anti-nerve agents include pyridostigmine and pralidoxime chloride. Examples of agents useful in the invention are listed below.

By active agent it is meant that the agent, once coupled to a biological tissue *in vivo* or *in vitro*, has, maintains or can be released to have a desired activity such as a desired physiological activity or therapeutic activity. Examples of active agents are pharmaceutical agents, sunscreen agents, insecticides, bactericides, fungicides, etc. In some embodiments,

the active agent is not a cosmetic agent. In other embodiments, the active agent is not a labeling agent such as a diagnostic agent. Compounds of Formula I are intended for a variety of uses, including but not limited to agent delivery and tissue sealing, provided their application to a body tissue is non-toxic.

According to the invention, the agents are linked to proteinaceous material. When used in vivo, the agents are preferably conjugated to a body tissue via the reactive molecule(s). Particularly important body tissues as sites of attachment are the integument (including specifically skin, nails, hair, mucous membranes and the surface of the eye), internal organs, internal tissue and wound beds. In *in vitro* applications, the tissue may be a body tissue, a tissue or cell isolate, isolated proteins, synthetic proteins, cell cultures and the like for use, for example, in assay systems according to the invention.

In certain embodiments, conjugates of agents and reactive moieties are applied, for example, to a body tissue. The agents are then covalently linked to that tissue through the reactive moieties. Reactive moieties useful in the invention are those of Group A (and derivatives thereof), N-hydroxyl succinimide and N-alkyl maleimide, all of which can be used as monofunctional reactive molecules.

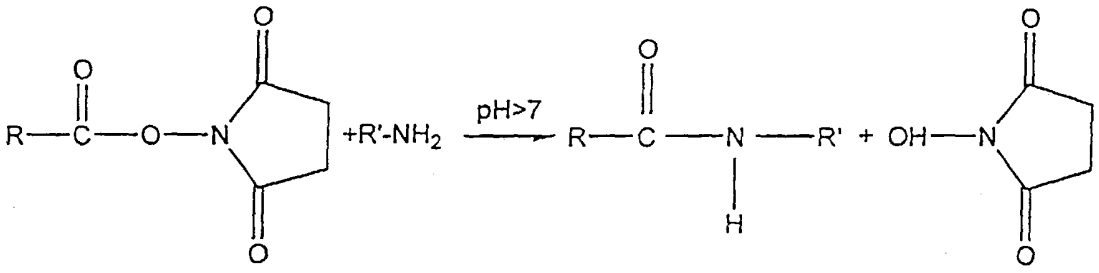
Other reactive molecules useful to the invention are those which are bifunctional, examples of which include, but are not limited to, bis-N-hydroxy-succinimide and bis-N-alkyl-maleimide. Formula II compounds, which include these latter two compounds, generally have the following structure:

Formula II

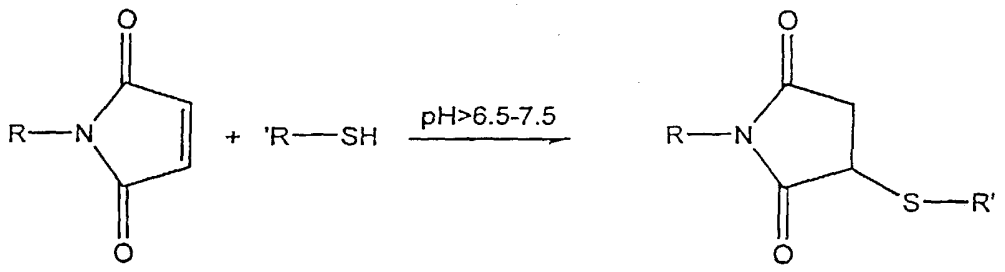
X_1 -- L -- X_2

wherein X_1 and X_2 are reactive moieties independently selected from Group A, N-hydroxy-succinimide, and N-alkyl-maleimide (or derivatives thereof); and L is a linking molecule. Reactions of N-hydroxy-succinimide and N-alkyl-maleimide with their respective targets are shown below:

N-hydroxyl succinimide ester reaction scheme



maleimide reaction scheme



As used herein, a "bifunctional reactive molecule" or a "bifunctional reactive compound" is one which possesses at least two reactive moieties. The reactive moieties need not be the same and they may react with different groups. Bifunctional reactive compounds may take the form of Formula I, Formula II, and Formula III compounds, provided both X_1 and X_2 are present. Formula I and Formula III compounds embrace bifunctional reactive compounds which are capable of agent delivery. Formula II compounds are generally not used for agent delivery. All bifunctional reactive molecules are capable of linking two separate entities, such as for example two tissues, a microparticle and a tissue, or an agent and a tissue.

Typically the agents used according to the invention are not themselves, in their native form, able to covalently attach to proteinaceous materials.

As used herein, a conjugate means two entities stably bound to one another by any physiochemical means. It is important that the nature of the attachment be of such a nature that it does not impair substantially the effectiveness of the agent or the substrate binding ability of the linking molecule, or the reactivity of any remaining reactive molecule. Keeping these parameters in mind, any linkage known to those of ordinary skill in the art may be employed including covalent or noncovalent. Covalent linkage is preferred. Such means and methods of attachment are well known to those of ordinary skill in the art.

The compounds of Formula I, II and III also incorporate a linker which can be used to tether or simply join the agent (which may be provided as a microparticle) and the reactive moiety. As used herein, "linker" and "linking molecule" are used interchangeably. One embodiment involves linkers that are polymers. The polymer can be a homopolymer or a heteropolymer.

In constructing compounds of Formulas I, II and III, it may be desirable to tether the linking molecule to the active agent (or the microparticle) via a spacer. This can remove, for example, any problems that might arise from steric hindrance. These spacers can be any of a variety of molecules, preferably nonactive, such as straight or even branched carbon chains of C_1-C_{30}, saturated or unsaturated, phospholipids, amino acids, and in particular glycine, and the like, naturally occurring or synthetic. Additional spacers include alkyl and alkenyl carbonates, carbamates, and carbamides. These are all related and may add polar functionality to the spacers such as the C_1-C_{30} previously mentioned. As used herein, the linkers of Formulae I, II and III may be spacers.

The conjugations or modifications described herein employ routine chemistry, which chemistry does not form a part of the invention and which chemistry is well known to those skilled in the art of chemistry. The use of protecting groups and known linkers such as mono and heterobifunctional linkers are well documented in the literature and will not be repeated here.

Attachment of the reactive moiety to the agent (or the microparticle) according to the invention thus need not be direct attachment. The components X and A of the compositions of the invention may be provided with functionalized groups to facilitate their attachment to one another and/or linker groups may be interposed between these components to facilitate their attachment. In addition, the components of the compositions of the present invention may be synthesized in a single process, whereby the components could be regarded as one and the same entity.

The linker molecule thus may contain functional groups for joining the X to the A, selected from the group consisting of a carboxylate group, an amino group, a sulfhydryl group, an imidazole group, an alkene group (a carbon atom double bonded to another carbon atom), an acyl halogen group, e.g., an acylchloride, and CH_2X, wherein X represents a halogen (e.g., the two binding moieties are linked when a nucleophilic group displaces the halogen from the functional group of the CH_2X linker molecule). Additionally the linker molecules may be of varying length spacer segments (linker molecules). Bifunctional linker molecules, as mentioned above, are also useful in the invention. A wide assortment of dicarboxylic spacer linker molecules are commercially available (see below for discussion). This includes linker molecules which have various internal heteroatoms and other functional groups, in addition to the terminal carboxylic groups, e.g., ethylene glycobissuccinate.

Using the linker ethylene glycobissuccinate (instead of adipic acid) provides a bivalent compound with a spacer of about twice the length of the adipoyl moiety. Also, the internal heteroatoms may confer improved water solubility over a straight chain hydrocarbon of similar length.

Chemical cross-linkers are valuable tools for scientists and are discussed in numerous books and catalogues, e.g., Pierce Catalog and Handbook, Rockford, Ill.

Reactivities of Different Chemical Groups

1. Imidoester Cross-linkers

Imidoester homobifunctional cross-linkers were among the first used to immobilize proteins onto solid-phase supports. They were used extensively for the study of protein structure and molecular associations in membranes. Although these cross-linkers are still used in protein subunit studies and solid-phase immobilization, they have been steadily replaced by the more stable, more efficient homobifunctional NHS-ester cross-linkers. Homobifunctional imidoesters maintain the net electronic charge on protein after cross-linking. Spacer arm lengths range from about 8.6 A to about 11.9 A. Imidoester cross-linkers react rapidly with amines at alkaline pH, but they have short half lives.

Imidoesters are also very useful for protein-protein cross-links. These cross-linkers can penetrate cell membranes and cross-link proteins within the membrane to study membrane composition, structure and protein-protein and protein-lipid interactions. Imidoesters are also useful for oligomer formation. For example, cross-linking proteins to form oligomers may reveal if a bivalent, dimeric or trimeric form of the protein is responsible for activity.

2. N-Hydroxysuccinimide-Esters (NHS-esters)

NHS-esters yield stable products upon reaction with primary or secondary amines. Coupling is efficient at physiological pH, NHS-ester cross-linkers are also more stable in solution than their imidate counterparts. Homobifunctional NHS-ester conjugations are commonly used to cross-link amine-containing proteins in either one-step or two-step reactions.

Primary amines are the principle targets for NHS-esters. Accessible α-amine groups present on the N-termini of proteins react with NHS-esters and form amides. However, because α-amines on a protein are not always available, the reaction with side chains of amino acids become important. While five amino acids have nitrogen in their side chains, only the ε-amines react significantly with NHS-esters. A covalent amide bond is formed when the NHS-ester cross-linking agent reacts with primary amines, releasing N-hydroxysuccinimide.

3. Coupling through Sulfhydryl Groups

Coupling through sulfhydryl groups is advantageous because it can be site-directed, yield cleavable products and allow for sequential coupling. A protein in a complex mixture can be specifically labeled if it is the only one with a free sulfhydryl group on its surface.

a. Maleimides

The maleimide group is specific for sulfhydryl groups when the pH of the reaction mixture is kept between pH 6.5 and 7.5. At pH 7, the reaction of the maleimides with sulfhydryls is 1000-fold faster than with amines. Maleimides do not react with tyrosines, histidines or methionines.

b. Haloacetyls

The most common used α-Haloacetyls react with sulfhydryl groups at physiological pH. The reaction of the iodoacetyl group with a sulfhydryl proceeds by nucleophilic substitution of iodine, with a thiol producing a stable thioether linkage. Selectivity for sulfhydryl groups is ensured by using only a slight excess of the iodoacetyl group over the number of sulfhydryl groups at pH 8.3. In the absence of free sulfhydryls, or if a gross excess of iodoacetyl group is used over the number of sulfhydryls, the iodoacetyl group can react with other amino acids.

c. Pyridyl Disulfides

Pyridyl disulfides react with sulfhydryls groups to form a disulfide bond. Pyridine-2-thione is released as a by-product of this reaction. These reagents can be used as cross-linkers and to introduce sulfhydryl groups into proteins.

4. Coupling Through Carboxyl Groups: Carbodiimides

Carbodiimides couple carboxyls to primary amines or hydrazides, resulting in formation of amide or hydrazone bonds. Carbodiimides are unlike other conjugation reactions in that no cross-bridge is formed between the molecules being coupled. Carboxy termini of proteins can be targeted, as well as glutamic and aspartic acid side chains. In the presence of excess cross-linker, polymerization is likely to occur because proteins contain carboxyls and amines. No cross-bridge is formed, and the amide bond is the same as a peptide bond, so reversal of the cross-linking is impossible without destruction of the protein. EDC (Pierce Co.) reacts with carbocyclic acid group and activates the carboxyl group, allowing it to be coupled to the amino group (R_4NH_2) in the reaction mixture.

5. Nonselective Labeling: Arylazides

A photoaffinity reagent is a compound that is chemically inert but becomes reactive when exposed to ultraviolet or visible light. Arylazides are photoaffinity reagents that are photolyzed at wavelengths between 250-460 nm, forming a reactive aryl nitrene. The aryl nitrene reacts nonselectively to form a covalent bond. Reducing agents must be used with caution because they can reduce the azido group.

6. Nonselective Labeling

a. Arginine Specific Cross-linkers

Glyoxals are useful compounds for targeting the guanidinyl portion of arginine residues. Glyoxals will target arginines at mildly alkaline pH. There is some cross-reactivity (the greatest at higher pH) with lysines.

b. Carbonyl Specific Cross-Linkers

Carbonyls (aldehydes and ketones) react with amines and hydrazides at pH 5-7. The reaction with hydrazides is faster than with amines, making this useful for site-specific cross-linking. Carbonyls do not readily exist in proteins; however, mild oxidation of sugar moieties using sodium metaperiodate will convert vicinal hydroxyls to aldehydes or ketones.

As mentioned above, specific examples of joining a reactive group X to an agent A include those wherein bifunctional linker molecules are used. The linker molecules may be homobifunctional or heterobifunctional, depending upon the nature of the molecules to be conjugated. Homobifunctional cross-linkers have two identical reactive moieties. Heterobifunctional cross-linkers are defined as having two different reactive moieties that allow for sequential conjugation reaction. Various types of commercially available cross-linkers are reactive with one or more of the following groups: primary amines, secondary amines, sulphydryls, carboxyls, carbonyls and carbohydrates. Examples of amine-specific cross-linkers are bis(sulfosuccinimidyl) suberate, bis[2-(succinimidooxycarbonyloxy)ethyl] sulfone, disuccinimidyl suberate, disuccinimidyl tartarate, dimethyl adipimate×2 HCl, dimethyl pimelimidate×2 HCl, dimethyl suberimidate×2 HCl, and ethylene glycolbis-[succinimidyl-[succinate]]. Cross-linkers reactive with sulfhydryl groups include bismaleimidohexane, 1,4-di-[3'-(2'-pyridyldithio)-propionamido)] butane, 1-[p-azidosalicylamido]-4-[iodoacetamido]butane, and N-[4-(p-azidosalicylamido) butyl]-3'-[2'-pyridyldithio]propionamide. Cross-linkers preferentially reactive with carbohydrates include azidobenzoyl hydrazine. Cross-linkers preferentially reactive with carboxyl groups include 4-[p-azidosalicylamido]butylamine. Heterobifunctional cross-linkers that react with amines and sulfhydryls include N-succinimidyl-3-[2-pyridyldithio]propionate, succinimidyl[4-iodoacetyl]aminobenzoate, succinimidyl 4-[N-maleimidomethyl] cyclohexane-1-carboxylate, m-maleimidobenzoyl-N-hydroxysuccinimide ester, sulfosuccinimidyl 6-[3-[2-pyridyldithio]propionamido]hexanoate, and sulfosuccinimidyl

4-[N-maleimidomethyl]cyclohexane-1-carboxylate. Heterobifunctional cross-linkers that react with carboxyl and amine groups include 1-ethyl-3-[[3-dimethylaminopropyl]-carbodiimide hydrochloride. Heterobifunctional cross-linkers that react with carbohydrates and sulfhydryls include 4-[N-maleimidomethyl]-cyclohexane-1-carboxylhydrazide×2 HCl, 4-(4-N-maleimidophenyl)-butyric acid hydrazide×2 HCl, and 3-[2-pyridyldithio]propionyl hydrazide. The cross-linkers are bis-[B-4-azidosalicylamido)ethyl]disulfide and glutaraldehyde. Amine or thiol groups may be added at any nucleotide of a synthetic nucleic acid so as to provide a point of attachment for a bifunctional cross-linker molecule. The nucleic acid may be synthesized incorporating conjugation-competent reagents such as Uni-Link AminoModifier, 3'-DMT-C6-Amine-ON CPG, AminoModifier II, N-TFA-C6-AminoModifier, C6-ThiolModifier, C6-Disulfide Phosphoramidite and C6-Disulfide CPG (Clontech, Palo Alto, CA).

In constructing conjugates, it also may be desirable to attach the agent to the linking molecule by a bond that cleaves under normal physiological conditions or that can be caused to cleave specifically upon application of a stimulus such as light, whereby the agent can be released. In certain instances, the agent may be inactive in its conjugated form and activated only when released. In other instances, the agent would be released to exert an activity remote from its point of attachment to the body tissue. In still other instances, the agent would be released in a sustained fashion, to prolong the release of the agent versus an agent applied to tissue but not covalently coupled to the tissue (or part of a microparticle). Readily cleavable bonds include readily hydrolyzable bonds, for example, ester bonds, amide bonds and Schiff's base-type bonds. Bonds which are cleavable by light are well known.

Noncovalent methods of conjugation may also be used. Noncovalent conjugation includes hydrophobic interactions, ionic interactions, high affinity interactions such as biotin-avidin and biotin-streptavidin complexation and other affinity interactions. In one embodiment, a molecule such as avidin is attached to a linking molecule (which is attached to a reactive moiety). This conjugate, once attached to tissue according to the invention, then becomes a universal linking moiety for any agent attached to a biotin molecule.

As mentioned above, the reactive compounds may be part of a microparticle such as a microsphere or a microcapsule (of micrometer and nanometer size), and the agent may be contained in the microparticle, either physically entrapped therein, covalently bonded thereto or otherwise physiochemically attached to the microparticle. The methods for manufacturing

microparticles according to the prior art are well documented and do not form a basis for the present invention. Examples of microspheres, nanospheres, microcapsules and nanocapsules and their method of manufacture may be found in U.S. Patent 5,075,019, PCT WO95/24929, PCT WO94/23738 and PCT WO/97/03657, the disclosures of which are incorporated herein by reference.

To be most useful, the microparticles of the invention possess reactive moieties on their surface (i.e., surface available reactive moieties). Reactive moieties include the reactive moieties of Group A, N-hydroxyl-succinimide, and N-alkyl maleimide and derivatives thereof, as well as any of the reactive moieties described herein. Microparticles may also possess on their surface reactive compounds (which comprise such reactive moieties). Such reactive compounds include both monofunctional and bifunctional compounds of Formula I, Formula II and Formula III The microparticles of the invention contain an agent which when released from the microparticle provides prophylactic, therapeutic or cosmetic benefit to an external body surface with which it is in contact. The microparticles of the invention are intended for use on a proteinaceous surface including an external body surface such as skin, hair or nails. Microparticles which remain attached to the external surface and which do not degrade substantially throughout the course of treatment (e.g., days or weeks) are most useful in the invention. Any microparticle that contains an agent (as described herein) and that can hold (as a result of the covalent binding described herein) and release the agent onto an external surface (e.g., a skin surface) for a period of time sufficient for the active agent to achieve its prophylactic, therapeutic or cosmetic purpose is useful in the invention. Microparticles commonly effect delivery of agents by way of diffusion, or by degradation or erosion. Examples of diffusional systems in which the active agent permeates at a controlled rate from a polymer are described in U.S. Patents 3,854,480, 5,133,974 and 5,407,686. Examples of erosional systems in which the active agent is contained within a matrix which in turn erodes with time are described in U.S. Patent 4,452,775, 4,675,189 and 5,736,152.

The invention provides microparticles which are either biodegradable or non-biodegradable. The term "biodegradable" as used herein refers to the ability of a substance (in this case, a microparticle) to degrade in vivo (e.g., upon contact with external surfaces such as the skin or upon entry into the body). Commonly, biodegradable microparticles are made from polymers having bonds which are easily hydrolyzed once in contact with a physiological environment.

According to the present invention, covalent linkage of the microparticle to the skin, hair or nails is desired. It is the covalent linkage which keeps the microparticles on the skin for the desired time, preferably in a layer, to achieve uniform and extended release of the active agent as desired. If the microparticles degrade too quickly, or degrade when contacted with a detergent such as soap, then the uniform distribution and extended release will be undermined. If degradation is slow or if degradation can occur independent of covalent attachment (such as degradation within a shell), then degradation can be acceptable. Thus, biodegradable microparticles are embraced by some aspects of the invention. Preferably, the biodegradable microparticles degrade substantially only after the period of time corresponding to the treatment (e.g., days or weeks) in order to ensure sufficient delivery of the active agent to the skin surface.

Microparticles that are differentially biodegradable are also useful in the invention. A "differentially biodegradable" microparticle is one which does not degrade uniformly throughout its volume. It may instead degrade initially in an internal or core region, as an example. Internally degradable microparticles may be formed by coating biodegradable cores with non-biodegradable porous films or shells. The microparticle may alternatively degrade from the outer surface, however, it would still be necessary that a sufficient amount of reactive moieties remains covalently attached at the surface and extending within the microparticle even throughout the portion of the degradation process during which covalent attachment of the microparticle is desired. This can be achieved, for example, by a microparticle which is covalently crosslinked internally. In important embodiments, the microparticles are substantially non-biodegradable at their point of attachment to the skin surface over the period of time during which covalent attachment is desired.

Another type of microparticle which is useful to the invention is one which is non-biodegradable. A non-biodegradable microparticle is one which does not degrade upon exposure to a physiological environment or temperature. As mentioned above, such non-biodegradable particles release active agent by diffusion. In important embodiments, the microparticles are substantially non-biodegradable during the treatment period, which may last for several days to several weeks or completely non-biodegradable. In this instance, the microparticles will simply be sloughed off along with the dead skin cells to which they are attached. As is well known to those of ordinary skill in the art, the outermost portion of the skin (to which the microparticles will be attached in some instances) is not living and is

sloughed off and replaced completely every 10 to 14 days. In some embodiments, a subset of microparticles having amines or lysines are non-biodegradable.

The microparticles of the invention may be synthesized using naturally occurring or non-naturally occurring polymers. Non-naturally occurring polymers are referred to herein as synthetic polymers. Naturally occurring polymers include nucleic acids, peptides, polypeptides, carbohydrates, alginate, polysaccharides (e.g., dextran, cellulose and glycogen), lipopolysaccharides, chitosan, chitin, peptidoglycans, starch, glycosaminoglycans, collagen, rubber (cis-1,4-polyisoprene), guayule (Parthenium argentatum), collagen, chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art), albumin and other hydrophilic proteins, zein and other prolamines and hydrophobic proteins, copolymers and mixtures thereof.

The microparticles of the invention may contain natural, synthetic or chimeric polymers provided that, in the formed microparticles, such polymers are their constituent subunits do not saturate, occupy or otherwise interfere with the availability of all reactive moieties required for covalently attaching the microparticles to the body tissue. Thus, the microparticles may be synthesized and may contain a variety of polymers and other compounds, provided that there still remains an amount of reactive moieties that are surface available sufficient for covalently attaching the microparticles to the body tissue.

The microparticles may further comprise one or more synthetic polymers or co-polymers. As used herein, the term "synthetic" refers to a substance which is not naturally occurring. Exemplary synthetic polymers include, but are not limited to, polyamides, polycarbonates, polyalkylenes, polysulfones, poly(2-sulfobutyl-vinyl alcohol)-graft-poly(D,L-lactic-co-glycolic acid), poly-hydroxyalkanoates, polyalkylene glycols, polyalkylene oxides, polyalkylene terepthalates, polydimethylsiloxane polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, silicones, polyglycolic acid (PGA), polylactic acid (PLA), copolymers of lactic and glycolic acids (PLGA), polyanhydrides, polyorthoesters, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes and co-polymers thereof, alkyl cellulose, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, polymers of acrylic and methacrylic esters, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxy-propyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxylethyl

cellulose, cellulose triacetate, cellulose sulphate sodium salt, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), polyethylene, polypropylene, poly(ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl alcohols), polyvinyl acetate, poly vinyl chloride, polystyrene and polyvinylpyrrolidone.

Still other microparticles may be comprised of chimeric polymers of synthetic and naturally occurring residues. "Chimeric polymers" as used herein, refer to polymers of different residues or units. For example, a chimeric polymer may contain amino acid and non-amino acid residues, or it may contain natural and synthetic residues. As used herein, a residue in a polymer refers to (and may be used interchangeably with) a unit of a polymer. Examples of a polymer residue (i.e., a polymer unit) include an amino acid in a peptide and a nucleotide in a nucleic acid. Non-amino acid residues such as saccharides, fatty acids, sterols, isoprenoids, purines, pyrimidines, derivatives or structural analogs of the above, or combinations thereof and the like may be used. Non-naturally occurring non-amino acid substitutes include but are not limited to 2-azetidinecarboxylic acid, pipecolic acid, S-ethylisothiourea, 2-NH_2-thiazoline and 2-NH_2-thiazole.

The microparticles of the invention may contain natural, synthetic or chimeric polymers provided that such polymers or their constituent subunits do not saturate all reactive moieties required for covalently attaching the microparticles to the body tissue. Thus, the microparticles may be synthesized using, and may contain, a variety of polymers and other compounds, provided that there still remains an amount of reactive moieties, that are surface available, sufficient for covalently attaching the microparticles to the body tissue.

The natural, synthetic and chimeric polymers may themselves be biodegradable or non-biodegradable, as intended herein. Examples of biodegradable polymers include synthetic polymers such as polymers of lactic acid and glycolic acid, polyanhydrides, poly(ortho)esters, polyurethanes, poly(butic acid), poly(valeric acid), and poly(lactide-cocaprolactone), and natural polymers such as those listed herein. In general, these materials degrade either by enzymatic hydrolysis or exposure to water *in vivo,* by surface or bulk erosion. The polymers may optionally be in the form of a hydrogel that can absorb up to

about 90% of its weight in water and further, optionally may be crosslinked with multivalent ions or other polymers.

Examples of non-biodegradable synthetic polymers include latex, polystyrene, polystyrene derivatives, poly-N-ethyl-4-vinylpyridinium bromide, silicone, polypropylene, ethylene vinyl acetate, poly(meth)acrylic acid, polymethylacrylate, polyamides, copolymers and mixtures thereof. U.S. Patent 5,861,149 discloses methods for making non-biodegradable microparticles which can be used in the present invention. Polystyrene particles useful in the invention are commercially available from a variety of manufacturers including Polysciences, Inc. (Warrington, PA), Seradyn (Indianapolis, IN) and Dynal.

The microparticles may also be formed from or may include non-polymer moieties such as lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono- di- and tri-glycerides.

The microparticles may be made from organic and/or inorganic substances. The majority of polymers listed above are organic. Examples of inorganic substances include but are not limited to polyphosphate, zirconia-silica (ZS), $Si(OC_2H_5)_4$, $Al(NO_3)_3 \times 9H_2O$, $AgNO_3$, HNO_3, poly(phenylphosphinoborane) (an inorganic analogue of polystyrene) and PRIMM.

The polymer and non-polymers which make up the microparticles may be crosslinked, but need not be. Crosslinking agents include chemicals such as glutaraldehyde, dithiobis(succinimidyl) propionate, carbodiimide, and N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), 1,4-Bis(acryloyl)piperazine, N-Hydroxysulfosuccinimide, as well as electromagnetic radiation such as UV radiation. A wide variety of crosslinking agents suitable to the various chemistries of the microparticles described herein are commercially available from manufacturers such as Pierce Chemical Co. (Rockford, IL) and Sigma Aldrich (St. Louis).

In some embodiments, the microparticles may be predominantly composed of one or more polymers. A blend of natural and synthetic polymers may be used in microparticle synthesis. The microparticles may have an external coating composed of the same or a different polymer or non-polymer substance. As an example, the microparticle may be composed internally of polystyrene and an active agent and may have an exterior coating (preferably covalently attached) of a substance rich in the reactive moieties useful in the invention. In other related embodiments, more than one polymeric or non-polymeric substance, or a combination thereof, may be commingled prior to microparticle formation,

resulting in their combined presence both internally and on the external surface of the microparticle.

The compounds of Formula I, Formula II or Formula III may be incorporated into the microparticles at the time of synthesis or, alternatively, they may be linked to the surface of a pre-formed microparticle. In another embodiment, the microparticles, once formed, may be coated with a suspension of Formula I, II or III compounds. Formula II compounds (and bifunctional reactive compounds of Formula III) may be used together with microparticles by applying these compounds to the body tissue, applying the microparticles to the body tissue, and allowing crosslinking to occur. In this latter embodiment, one reactive moiety of the compound crosslinks to the tissue while the other crosslinks to the microparticle. Microparticles having surface available amines or thiols are most preferred in these embodiments. The bifunctional reactive compounds may be applied to the body tissue, preferably before, but also simultaneously or following the application of the microparticles.

In still other embodiments, the agent is present in the microparticle and is not covalently attached to the reactive moieties of Group A, N-hydroxy succinimide or N-alkyl maleimide. Still, the microparticle possesses on its surface these reactive moieties and is capable of covalently attaching to the body tissue. In these embodiments, rather than being attached to the agent, the reactive moieties of Group A may be attached to a substituent of the microparticle, such as a polymer, or to a linker.

As used herein, the term "microparticle" embraces particles, spheres and capsules of both nanometer and micrometer sizes (i.e., microparticles, microspheres, nanoparticles, nanospheres, microcapsules and nanocapsules). The microparticles may adopt a variety of shapes including regular shapes such as spheres and ellipses as well as non-regular shapes. Additionally, the surface may be, but need not be, smooth. The microparticles may be hollow with the agent stored in the core of the shell, in which case, they may be referred to as microcapsules or nanocapsules. Alternatively, they may be porous with the agent dispersed throughout the solid polymeric or non-polymeric matrix, in which case they may be referred to as microspheres or nanospheres. A porous microparticle is one having internal, potentially interconnected channels (or pores) which are preferably open to the external surface of the particle. Methods for synthesizing hollow and porous microparticles are well known in the art. Porous microparticles are generally made by the inclusion of a porogen during microparticle synthesis followed by its removal (e.g., through dissolution in an appropriate

solvent) and subsequent replacement with a solution containing the active agent. As provided herein, the porous microparticles may additionally have a coating comprising reactive moieties, while being internally void of these groups.

In some embodiments, it is recommended that the microparticle be less than five microns in size (i.e., any single dimension of the microparticle is less than 5 microns). The microparticle should be small enough so as to feel smooth if applied to the external body surface. In some embodiments, it is preferred that the particles be large enough to preclude their penetration into an external surface such as the skin. It has previously been reported that microparticles less than 100 microns are capable of penetrating the skin surface. In other embodiments, it is desired that the microparticles with surface available reactive moieties are small enough to penetrate the external surface, preferably up to but not including the layer of living cells. Thus, in some embodiments, the average size of the microparticle is less than 1 micron but greater than 100 nm, and in others, it is 100 nanometers to 500 nanometers. In still other embodiments, the average size of the microparticles is less than 100 nm in size, 20 nm to 90 nm in size, or 20 nm to 35 nm in size. In most instances, it may be undesirable for the microparticles to penetrate the living layer, and it is therefore intended that the microparticle remain in the cornified layer. It is believed that microparticles less than 1 nm, as well as others that are less than 5 nm could penetrate to the living layer, and thus should be avoided in most instances. However, it may be desirable for the particles to enter the cornified layer and thereby release their active agent which may diffuse into and thereby enter the living layer. Still, microparticles of an average size of 1 nm to 20 nm, 1 nm to 10 nm and in particular 5 nm to 10 nm may be desirable in some aspects of the invention. It is well within the realm of the ordinary artisan to determine the size of particles which are best suited to the various embodiments recited herein.

It also should be noted that size may be relatively uniform as in all the particles being of a certain size, or range or size may be mixed. Where it is desired to prevent the microparticles from penetrating the outer most surface of the epidermis, then all the microparticles should be at least a certain size (e.g., at least 100 nm). If it is desired that all microparticles penetrate the outer most surface of the epidermis, then they should be no larger than a certain size (e.g., no larger than 100 nm). It also may be desired to have a variety of sizes whereby the microparticles will penetrate to different extents depending on size, thereby forming a three dimensional "layer". Size will depend upon factors such as the agent to be

delivered, the condition being treated, the desired length of treatment, and other such factors well known to those of ordinary skill in the art. Appropriate size can be determined by no more than routine experimentation, trying different sizes to select the one or ones that are ideal for a particular purpose.

The microparticles are linked to proteinaceous material. When used *in vivo*, the microparticles are attached to a body tissue. Particularly important body tissues as sites of attachment are the integument (including specifically skin, nails, hair, mucous membranes and the surface of the eye), internal organs, internal tissue and wound beds. In *in vitro* applications, the tissue may be a body tissue, a tissue or cell isolate, isolated proteins, synthetic proteins, cell cultures and the like for use, for example, in assay systems according to the invention. In important embodiments, the body tissue is a skin, nail or hair surface.

Due to the use of these particles on skin, hair and nails, it is important that some of these particles be resistant to the action of detergents, such as those regularly used on these surfaces (e.g., hand, face and body soap, and shampoo). Thus, in some embodiments, the microparticles are water insoluble and, preferably, detergent insoluble (i.e., neither the microparticle nor the bond between the microparticle and the external surface are adversely affected by exposure to detergents, such as hand, body and hair soap). Many of the organic polymers listed herein are water insoluble. It is well within the realm of the ordinary artisan to determine which of these are preferred for making water insoluble particles. Microparticles may be rendered substantially detergent insoluble by cross-linking or by bonding of non-covalent nature that similarly renders the microparticle insoluble. If cross-linking is used, it is recommended that the reactive moieties of Group A, N-hydroxy succinimide or N-alkyl maleimide are protected to prevent them from participating in the crosslinking, that a crosslinking agent be used which does not involve these reactive moieties or that the reactive moieties be attached to the microparticle after such cross-linking. In another embodiment, the microparticles can be made more resilient to detergent treatment by the incorporation of fluorinated steroids as taught in U.S. Patent 4,927,687.

To be useful, the microparticles must possess reactive moieties, such as those of Group A, N-hydroxy-succinimide, N-alkyl-maleimide, or any of the reactive compounds described herein as compounds of Formulae I, II or III. The reactive moieties may be provided by any compound which contains them, including, but not limited to, compounds of Formulae I, II and III.

As suggested in the foregoing discussion, it is important that these reactive moieties be accessible to the body tissue (e.g., the skin) to which the microparticles are to be bound. The reactive moieties must be sufficiently exposed, and the "backbone" to which they are attached preferably sufficiently flexible, to react with and form a covalent bond with reactive molecules on the contacted surface (such as lysines or cysteines). Reactive moieties which are present on the surface of the microparticles are likely to be accessible, and thus such "surface available" reactive moieties are generally preferred.

Surface available reactive moieties may be "free" or "fixed." Free surface available reactive moieties include those which are present on a free, unconstrained end of a polymeric or non-polymeric substance, present at the surface of the microparticle. The free, unconstrained end of the polymeric or non-polymeric substance may be any length, provided the reactive moieties contained therein are capable of reacting with the body tissue (e.g., the skin). Free reactive moieties also embrace those which are non-complexed. A non-complexed reactive moiety is one which is not in physical association with another moiety to the extent that it is precluded from contacting and being covalently attached to a reactive group on, for example, the skin. Fixed reactive moieties may also be useful in the invention, provided they are sufficiently flexible to bind to skin surface reactive moieties. Thus, a reactive moiety may be present in a loop of a polymer the ends of which are both bound to the surface of the microparticle. As long as the loop is long enough and flexible enough to allow the reactive moieties to contact and react with the body tissue (e.g., skin), this type of "fixed reactive moiety" will be useful.

The surface available reactive moieties must also be present in an amount sufficient to attach covalently the microparticles to the skin.

Polymeric and non-polymeric substances from which the microparticles are synthesized may inherently possess the necessary reactive moieties (or molecules), or they may be derivatized either prior to or following microparticle formation to possess such groups. Alternatively, the microparticles may be formed of substances lacking reactive moieties and then coated with a substance which contains these moieties. As another alternative, the compounds of Formula I, II or II may be interspersed into the microparticle matrix during synthesis so that such compounds are present but not necessarily covalently bonded to the microparticle matrix. In another variation, the reactive moieties may also be linked to the surface of the microparticle after microparticle formation. As an example, the

surface may be prepared or treated to contain amine or thiol moieties, after which it is exposed to an excess of a bifunctional reactive compound such as a Formula II compound having a reactive moiety which reacts with amines or thiols. Preferably, the microparticle is treated so as to have either amines or thiols on its surface, and even more preferably, the bifunctional reactive molecule has one reactive moiety which reacts with amines and another which reacts with thiols. Thus, as an example, the microparticle may be one treated to have thiol groups on its surface, and a bifunctional reactive molecule is one with a Michael acceptor moiety and a carbonyl moiety. The Michael acceptor moiety will react with the thiol groups on the microparticle surface, thereby covalently attaching the microparticle to the bifunctional reactive molecule. The resulting conjugate may then be applied to a body tissue and covalently attached there using the remaining reactive moiety in the bifunctional compound. Polymers or other backbones rich in amines or thiols also can be covalently attached at the surface of the microparticle using homo and heterobifunctional crosslinkers. It further is envisioned that such polymers (or other backbones carrying reactive moieties) can be tethered to the surface of a microparticle by hydrophobic bonding. The manufacture of such microparticles is well within the realm of the ordinary artisan.

The methods for manufacturing a variety of microparticles according to the prior art are well documented. The present invention differs from those of the prior art, in part, in that the polymers or non-polymers of the microparticle themselves contain or are derivatized (including by tethering) to contain reactive moieties such as those present in Group A, N-hydroxy succinimide and N-alkyl maleimide, and the like at the surface, thereby being available for covalent bonding to the body tissue.

Preferred polymers are polymers bearing multiple reactive moieties, such as those described herein. Additionally, polymers having such reactive moieties spaced at discrete intervals are also useful in the invention. It has been discovered, surprisingly, that the spacing of the reactive moieties can be important to achieving the results of the present invention. Thus, a further embodiment of the present invention involves microparticles comprising polymers having multiple units, which each bear a reactive moiety such as those described herein. The polymer can be a homopolymer or a heteropolymer. Polymers having reactive moieties may contain at least three reactive moieties spaced apart from one another at discrete intervals along the backbone of the polymer, separated by one or more backbone atoms. The polymer may comprise, or in some instances consist solely of, contiguous reactive moieties,

preferably at least 3, at least 4 and at least 5 such contiguous reactive moieties. Polymers of contiguous units, each carrying a reactive molecule, are preferred.

Another category of preferred polymer is those rich in units having reactive moieties, wherein the units may have the same or may comprise a combination of different reactive moieties. A polymer rich in units having reactive moieties is a polymer wherein at least 20% of the units of the polymer carry a reactive molecule, or wherein the polymer includes at least 3, preferably 4 and most preferably 5 separate and discretely spaced by a regular distance units having reactive moieties. In other embodiments, the polymer includes at least 10, at least 15 or at least 20 separate and discretely spaced units having reactive moieties. It should be understood, however, that a chain of as few as two units having reactive moieties can be attached to or tethered to an microparticle to render the microparticle capable of attaching to a body tissue. The polymers may also contain at least 30%, at least 40%, at least 50% or more of units having reactive moieties, depending upon the embodiment.

In constructing microparticles, it may be desirable to vary not only the number of surface available reactive moieties, but it also may be desirable to tether the reactive moieties to the microparticle via a spacer. This can remove, for example, any problems that might arise from steric hindrance, wherein access to the reactive moiety directly on the surface is hindered. These spacers can be any of a variety of molecules, preferably nonactive, such as straight or even branched carbon chains of C_1-C_{30}, saturated or unsaturated, phospholipids, amino acids, and in particular glycine, and the like, naturally occurring or synthetic. Additional spacers include alkyl and alkenyl carbonates, carbamates, and carbamides. These are all related and may add polar functionality to the spacers such as the C_1-C_{30} previously mentioned.

The polymers may also have termini (either amino or carboxy) that are predominantly rich in reactive molecules or in units having reactive moieties. Preferably, the termini are located on the surface of the microparticle. The terminus may be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 or more units at a terminal end of a polymer. The reactive moiety rich stretch of the polymer may also be located on a "loop" of a polymer which is present at the surface of a microparticle.

The reactive moieties of Group A, N-hydroxy-succinimide, N-alkyl-maleimide and the like are capable of reacting with amine groups (such as those present in lysine) and/or thiol groups (such as those present in cysteines). Consequently, the microparticles described

herein can also be made from or attached to polymers and non-polymers which contain amines and thiols, as described above. Polymers rich in amines include but are not limited to albumin and polylysine. Microparticles having surface available amines or thiols are preferably used together with bifunctional reactive compounds.

Thus, it is to be understood that all teachings provided herein relating to the manufacture and use of microparticles having "reactive moieties" (such as those of Group A compounds and the like), similarly apply to the manufacture and use of microparticles having amine and/or thiol groups, particularly those that are surface available. Microparticles having amine and/or thiol groups are particularly useful in embodiments in which bifunctional reactive molecules (such as bis-N-hydroxy-succinimide or bis-N-alkyl-maleimide) are applied to the body tissue (e.g., the skin), and microparticles are separately applied to the body tissue. One reactive moiety of the bifunctional molecule would attach to the body tissue and the other would attach to the microparticle having surface available amines or thiols. Although the bifunctional molecule could be premixed with the microparticle prior to application to the body tissue (depending upon the choice of surface available reactive moieties and the choice of reactive moieties in the bifunctional compound), it is preferred in some embodiments that each be applied to the body tissue separately. The order of application of the bifunctional molecule and the microparticle can be reversed. Embodiments in which one reactive moiety of the bifunctional compound reacts only with a microparticle and the other reactive moiety of bifunctional compound reacts only with the body tissue are preferred in some instances.

A number of different techniques exist for making microparticles, including phase separation, solvent evaporation, emulsification and spray drying. The following examples are intended to provide guidance in the synthesis of some microparticles of the invention.

Encapsulated microspheres made from poly(lactide-co-glycolide) and poly(ε-CBZ-L-lysine) and subsequently treated so as to expose surface reactive amino groups have been reported previously. (Zheng and Hornsby, 1999, Biotechnol. Prog. 15:763-767) Once the microspheres are formed using double-emulsification/solvent evaporation (Alonso, et al., 1993, Pharmacol. Res. 10:945-953), the carbobenzoxy (i.e., CBZ) protective groups are removed using either acid hydrolysis or lithium/liquid ammonia reduction, thereby exposing reactive amine groups. Lithium/liquid ammonia reduction is recommended if microsphere are desired, given its less harsh effect of the external surface of the microparticle. In addition, the lithium treatment was reported to be more effective in producing surface reactive amino

groups than was the acid hydrolysis procedure. If a solid surface particle (i.e., a microsphere) is desired, the lithium treatment may be preferred. In this latter method, the active agent may be added during the formation of the microparticles since the lithium treatment reportedly does not create pores in the surface of the particles and thus will not adversely affect the agent. If, on the other hand, a surface porous particle is desired, then the acid hydrolysis method may be preferred, provided the agent is either resistant to the acid treatment or is loaded into the particles following acid treatment.

A similar strategy may be used to produce non-biodegradable microparticles, by substituting poly(lactide-co-glycolide) with a non-biodegradable polymer such as those disclosed herein. In another variation of this method, a copolymer of lysine and a synthetic polymer such as, for example, poly(lactic acid-co-lysine) may be used alone to form the microparticles followed by mild acid hydrolysis or lithium treatment. Such lysine containing copolymers have been manufactured previously. (Barrera, et al., 1993, J. Am. Chem. Soc. 115:11010-11011) In yet a further variation, it may be possible to form particles from a biodegradable or a non-biodegradable polymer mixed with a CBZ-lysine rich polymer which is not poly-lysine or, alternatively, with short peptide or peptidomimetic backbone compounds which contain CBZ-protected aliphatic amines.

In another modification, microparticles may be made using the technique of Zheng and Hornsby but excluding poly-lysine. After being formed, the microparticles may be coated with a solution of poly(ε-CBZ-L-lysine). Commercially available microparticles such as those made from polyacrylamide, polyacrylate, polystyrene, or latex (Bio-Rad Laboratories (Richmond, CA), LKB Produkter (Stockholm, Sweden)) or those made from natural polymers such as agarose, crosslinked agarose, globulin, and liposomes (Bio-Rad Laboratories (Richmond, CA), Pharmacia (Piscataway, NJ), IBF (France)) can also be coated with CBZ-protected as well as non-protected lysine containing polymer solutions following agent loading. Microcapsule coating methods are known in the art.

To determine whether a microparticle generated according to the teachings herein is useful, a simple screening method is employed. The screening method involves selecting a microparticle and applying it, in an isolated form, to a proteinaceous material such as a body tissue, a body tissue isolate, or more preferably, a polymer rich in cysteine, a polymer rich in lysine or a polymer rich in cysteine and lysine. The microparticle is allowed to remain on the material for a time sufficient for forming covalent bonds with the tissue. Then it is

determined whether the microparticle covalently binds to the proteinaceous material. The microparticle may be loaded with a labeling agent such as a fluorescent dye or a fragrance. As applied to the screening assay, it is recommended that the labeling agent is covalently fixed to the microparticle such that no label escapes from the microparticle. This will ensure that any label detected on the external surface is indicative of a microparticle that is bound to the surface rather than a label which has exited a microparticle which itself was not capable of binding to the surface. In a further modification of this assay, once the microparticle is allowed to bind to the surface, the surface may be additionally washed with water and/or a detergent and then again tested for the presence of the microparticle. The amounts of materials and conditions employed for these assays are derivable from the examples below and, in general, can be derived by those of ordinary skill in the art without undue experimentation from, for example, the publication by Kahlem, et al., *Proc. Natl. Acad. Sci., USA*, Vol. 93, pp. 14580-14585, December, 1996.

Prior to contact with the body tissue, the microparticle is loaded with an agent, either physically entrapped therein, covalently bonded thereto or otherwise physiochemically attached to the microparticle. The active agent may be incorporated (i.e., "loaded") into the microparticle either at the time of, or after, microparticle formation, depending upon whether the microparticle formation process would be deleterious to the active agent. By active agent it is meant that the agent, once coupled to a body tissue (such as skin) *in vivo* or *in vitro*, either directly or indirectly via a microparticle, has, maintains or can be released to have a desired activity such as a desired physiological, prophylactic, therapeutic or cosmetic activity. Examples of agents are pharmaceutical agents, sunscreen agents, insecticides, bactericides, fungicides, etc. In certain embodiments, the active agent is not a labeling agent such as a diagnostic agent. In other embodiments, the agent is not a cosmetic agent.

In some, but not all, embodiments in which the microparticle comprises polylysine, the active agent is a non-nucleic acid active agent. A non-nucleic acid active agent, as used herein, refers to an active agent which is not a nucleic acid. In other embodiments, the active agent is a non-protein active agent. A non-protein active agent is an active agent which is not a protein (i.e., it is not composed exclusively of peptide linkages of amino acid residues or units).

In certain embodiments, the agent is a noncorneocyte, nonlabeling active agent. Specifically excluded in these particular embodiments are corneocyte proteins. In certain

embodiments, the agent also is a non-extracellular matrix protein agent. A non-extracellular matrix protein agent is one that is not an extracellular matrix protein. A nonlabeling active agent is one that is not simply a passive label with no function, when applied to a body tissue, other than being a label. Thus, specifically excluded in some embodiments are labeled corneocyte proteins, labeled fibronectin, labeled extracellular matrix proteins, putrescine, dansylcadaverine, 5-(biotinamido)-pentylamine, fluoresceincadaverine and the like.

Typically the agents used according to the invention do not themselves, in their native form, possess reactive moieties. If desired, however, such agents can be modified according to the invention to contain reactive moieties or alternatively and preferably, in some embodiments, they may be tethered or linked to a reactive moiety such as in Formula I. Alternatively, they may be modified so as to contain amine or thiol groups, particularly if they are to be used with a bifunctional reactive molecules such as those described herein. This may be accomplished, for example, by adding amine or thiol groups to the agent to form a "modified" agent, or by covalently coupling an amine or thiol group (in the form of lysine or cysteine, for example) to for a "conjugate."

The agent may be linked to the natural, synthetic or chimeric polymer or non-polymer. Such linkage may be covalent in nature. Preferably, any linkage between the active agent and another component of the microparticle is characterized by a bond that cleaves under normal physiological conditions or that can be caused to cleave specifically upon application of a stimulus such as light, whereby the agent can be released. Readily cleavable bonds include readily hydrolyzable bonds, for example, ester bonds, amide bonds and Schiff's base-type bonds. Bonds which are cleavable by light are well known. In certain instances, the agent may be inactive in its conjugated form and activated only when released. In other instances, the agent would be released to exert an activity remote from the point of attachment of the microparticle to the body tissue.

Noncovalent methods of conjugation may also be used. Noncovalent conjugation includes hydrophobic interactions, ionic interactions, high affinity interactions such as biotin-avidin and biotin-streptavidin complexation and other affinity interactions.

In some embodiments, it is preferred that the active agent is free and not linked to another component of the microparticle. In these latter embodiments, the release of the active agent from the microparticle is dependent upon the flow of (physiological) fluids into the porous network of the microparticle, the dissolution of the active agent in such fluids and the

exit of fluid and agent from the microparticle. Preferably, the agent would be released in a sustained fashion.

Active agents in an isolated form may also be used according to the invention. "Isolated" as used herein will depend upon the agent employed. In general, isolated means that the material is essentially free of other substances to an extent practical and appropriate for the intended use of the material. In the case of pharmaceuticals and cosmetics, the materials are likely to be substantially pure. In the case of proteins, the proteins are sufficiently pure and sufficiently free from other biological constituents of the host cells from which the proteins are derived so as to be useful in the methods according to the invention. Typically, such active agents will be at least 95% or more pure.

Agents are sometimes described as native agents herein. A native agent is one as it occurs in nature (isolated or synthesized to duplicate a naturally occurring molecule), without modification or conjugation as described herein.

As mentioned above, the body tissue, to which the agents and/or microparticles are to be applied, may be, but need not be, pretreated to facilitate the reaction with compounds of Formula I and II. Such treatments include washings, abrasive treatments including physical agents such as pumice, silica and oatmeal, enzymes such as papain, bromelins and the like and chemical agents such as alpha hydroxy acids and glycolic acids. The main object is to treat the body tissue so as to expose or create reactive cysteines and/or lysines. Likewise, as mentioned above, the body tissue may be pretreated by putting down a layer of reactive molecules, such as by applying to the body tissue polymers rich in lysine, cysteine or both lysine and cysteine or applying bifunctional reactive compounds. These materials may be attached to the body tissue by any conventional means, including for example attachment of polylysine to the tissue by transglutaminase.

It should be noted that cysteine, lysine, and polymers of cysteines and lysine are described above. As used herein, such terms embrace nonpeptidic multimers of cysteine and lysine whereby amino acid analogs are used to replace these amino acids in the polycysteine or polylysine substrates. Some well known classes of peptide mimetics and pseudopeptides are: azabicycloalkane amino acids; thiazabicycloalkane amino acids; oxazabicycloalkane amino acids; diazabicycloalkane amino acids. D-amino acids are an important embodiment.

In one embodiment some of the reactive moieties including the N-hydroxyl succinimide and maleimide reactive moieties can be used in a bis form to glue two tissues to

one another. When used according to this embodiment, the reactive molecules need not also carry an agent. Such compounds are shown in Formula II:

Formula II

X_1 --L -- X_2

wherein X_1 and X_2 are reactive moieties selected from Group A or N-hydroxyl succinimide or N-alkyl-maleimide, and the like. In some embodiments, X_1 and X_2 are identical. Examples of Formula II compounds include but are not limited to bis-N-hydroxyl succinimide and bis-N-alkyl-maleimide. Compounds of Formula II can be supplied to the surfaces of two tissues which then are held in contact with one another for a period of time sufficient to permit crosslinking the tissues to one another. In related aspects, compounds of Formula I and III can also be used to seal tissues together, provided that X_1 and X_2 are both present. In addition to sealing tissue, these latter compounds may also deliver agents to the tissues in the process.

The invention further provides methods of treating a subject to attach microparticles to a tissue of the subject by contacting a tissue of the subject with a microparticle having surface available reactive moieties and allowing the microparticles to remain in contact with the tissue for a time sufficient to permit a layer of microparticles to covalently attach to the tissue. The reactive moieties are present on the surface of the microparticle in an amount sufficient to attach the microparticle to the skin surface. The quantity of surface available reactive moieties which is a "sufficient amount" will vary depending upon a number of factors including, but not limited to, the number, quantity and accessibility of corresponding reactive groups on the body tissue, and the size of the microparticle. A sufficient amount of surface available reactive moieties can be achieved, for example, by increasing in the microparticles the number of residues which have the reactive moieties, or by increasing in the microparticles (and particularly at the surface) the number of reactive moieties by preventing their chemical reaction with other reactive moieties either intrinsic or extrinsic to the microparticle. Whether the particles have a "sufficient amount" of surface available reactive moieties can be tested as described herein. Preferably, the tissue is an external surface such as skin, nails or hair. In important embodiments, the tissue is a skin surface.

The method may also involve contacting the skin with a bifunctional reactive compound (e.g., a compound of Formula II) and contacting the skin with the microparticle, and allowing the bifunctional compound to remain in contact with the skin and allowing microparticles to remain in contact with the bifunctional compound for a time sufficient to permit a layer of microparticles to covalently attach to the skin (e.g., via the bifunctional compound).

As used herein, a subject may be a human, non-human primate, cow, horse, pig, sheep, goat, dog, cat, rabbit or rodent. In all embodiments, human subjects are preferred.

The subject to be treated according to the methods of the invention is one who will benefit from the treatment with the agents, conjugates and microparticles. Such treatment can be prophylactic, such as when the microparticles contain a sunscreen agent or a UV filter, or it can be therapeutic, such as when the microparticles contain an anti-fungal agent. Additionally, the subject may be one in need of cosmetic benefit, in which case the microparticles may contain a cosmetic such as a moisturizer or a skin tanning agent.

The term "contacting" as used herein refers to a physical interaction between the body tissue, such as for example the skin surface, and the agents, reactive compounds or microparticles (or between the bifunctional reactive compounds and the microparticles), or, alternatively, the suspension in which the agents, compounds or microparticles are provided. Preferably, "contacting" embraces placing the agents, compounds or microparticles in close enough proximity to the skin to allow for their attachment to the skin via the reactive moieties. In the case of microparticles, the reactive moieties are preferably those which are surface available. The agents, compounds or microparticles may be applied to the skin alone or, alternatively, they may be provided together with a pharmaceutically acceptable carrier. In some embodiments, microparticles may be applied to the skin along with a bifunctional compound, as described herein. In some embodiments, agents, compounds or microparticles can be provided in a formulation commonly intended for application to an external surface, such as a lotion, gel, ointment, jelly, cream, shampoo, detergent or spray (e.g., aerosol).

While many of the embodiments described herein refer to attachment or application of microparticles to a body tissue directly, it is to be understood that such embodiments also embrace situations in which a bifunctional compound is applied to the tissue prior to, simultaneously with, or following the microparticles.

After contacting the agents, compounds or microparticles with, for example, the skin surface, it is necessary to allow them to remain in contact with the skin surface for a time sufficient to permit a layer of agents, compounds or microparticles to covalently attach to the tissue. When the agents, compounds or microparticles are contacted with the skin surface they generally will distribute randomly throughout a volume above the skin surface, or if small enough in size, throughout a volume under the outermost layer of skin. This will also be the case should the agents, compounds or microparticles be provided in a topical formulation such as an ointment. Not all the agents, compounds or microparticles will contact the skin surface initially, however with time, a sufficient number will settle closer to the skin surface until the point where their reactive moieties will react with counterpart active molecules on the skin, resulting in a covalent bond that tethers the agents, compounds or microparticles to the skin. If the agents, compounds or microparticles are small enough, they will distribute randomly below the outermost layer of skin and preferably in proximity to the layer of living skin cells. A "sufficient number of microparticles" is that number required to provide an effective amount of the active agent to the tissue (e.g., the skin surface). In most cases, this will embrace the amount necessary to achieve a uniform distribution of the agent throughout the surface area of the tissue intended to be treated.

The agents, compounds or microparticles, whether applied to the tissue in an isolated form or as part of a formulation, are allowed to settle towards the tissue and thereby form a layer. A layer of agents, compounds or microparticles is that amount and distribution that is enough to provide distribution of active agent to, for example, the skin in amounts sufficient to achieve the prophylactic, therapeutic or cosmetic purpose of the agent. The agents, compounds or microparticles need not be evenly adjacent to one another in the layer, nor must they be in the same plane (as described herein) provided their distribution above, within or below the outermost layer of skin allows the active agent to be distributed sufficiently. As an example, when the active agent is a sunscreen, it is desirable that it be applied uniformly distributed over an entire area of skin in order to provide maximal effect. It may not be necessary, however, that for example the microparticles containing the sunscreen be physically touching each other, provided each microparticle is capable of providing sufficient amounts of the agent for a particular surface area. The same is true for the distribution of compounds containing sunscreens. As a further example, if the active agent is a cosmetic, it may be desirable to form a layer of microparticles over a defined surface area in order to

provide the cosmetic solely to the discrete area. The layer of agents, compounds or microparticles may be a volume of space over the tissue occupied by the agents, compounds or microparticles. The agents, compounds or microparticles may be, but need not be, in a planar arrangement. By a planar arrangement, it is meant that the agents, compounds or microparticles are equidistant from the surface of the tissue. Conversely, a non-planar arrangement indicates that the agents, compounds or microparticles are differentially spaced away from the surface of the tissue. The distance of the agent, compound or microparticle from the surface of the tissue may depend upon the location of the reactive moieties which have covalently linked to the tissue. If these are located on long pendent chains, the agent, compound or microparticle may not be contacting the tissue surface at all.

In some embodiments, it may be desired that the microparticles penetrate the skin to the deeper cornified layers but preferably not into the layer of living cells. Thus, rather than being located on the skin surface, the particles may be located within the cornified layer of the skin. In these latter embodiments, it may also be desirable to use microparticles which possess bifunctional compounds and amines and/or thiols on their surface so that microparticles crosslink with each other (i.e., covalent bonds may be formed between reactive moieties of Formula II compounds on one microparticle and amines or thiols on another) once the microparticles enter the cornified layers. The crosslinked microparticles may then become so large that they are unable to exit this layer and are thus retained there. In similar embodiments, the microparticles may all possess only amines or only thiols or a mixture of amines and thiols or alternatively, a mixture of microparticles some of which possess surface available amines and others which possess surface available thiols. The surface reactive moieties of the microparticles will dictate the optimal bifunctional molecules to use. As an example, if all the microparticles possess surface available amines, then the preferred bifunctional reactive molecule is one which has two reactive moieties which react with amines. In some embodiments, the microparticles may be those which degrade following the treatment period.

If the microparticles are provided to the skin surface as part of a formulation such as those listed above, it is important that the majority of the active agent does not exit (i.e., leach) from the microparticle and into the formulation prior to contact with the skin. Preferably, the active agent is not substantially soluble in the formulation. Instead, the agent will exit the microparticle only upon contact with the skin. This may occur if, for example,

the active agent is specifically soluble at higher temperatures (such as at the skin surface), or in the bodily secretions at the skin surface. Alternatively, the microparticle may be made from substances which are temperature or environment sensitive, so that contact with the skin but not necessarily with the formulation induces their disintegration and the subsequent release of the active agent. Thermosensitive polymers in the form of poly(ether-ester) block copolymers are reported by Cha et al., in U.S. Patent 5,702,717.

The agents, compounds or microparticles may optionally be combined with a pharmaceutically-acceptable carrier to form a pharmaceutical preparation. The term "pharmaceutically-acceptable carrier" as used herein means one or more compatible solid or liquid filler, diluents or encapsulating substances which are suitable for administration into a human. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions also are capable of being commingled with the agents of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficacy.

When administered, the pharmaceutical preparations of the invention are applied in pharmaceutically-acceptable amounts and in pharmaceutically-acceptably compositions. Such preparations may routinely contain salt, buffering agents, preservatives, compatible carriers, and optionally other therapeutic agents. When used in medicine, the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically-acceptable salts thereof and are not excluded from the scope of the invention. Such pharmacologically and pharmaceutically-acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, salicylic, citric, formic, malonic, succinic, and the like. Also, pharmaceutically-acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts.

The compositions of the invention should be applied under conditions which enhance the interaction between, and covalent attachment of, reactive moieties incorporated into Formula I and II compounds and proteinaceous material. Those conditions will depend upon the mode of delivery, the pH of the body tissue to the compound is applied, as well as the presence of other facilitating molecules which function to enhance such interactions.

Determining the most favorable conditions for such interactions is well within the realm of the ordinary artisan.

The mode of delivery typically will be topical. Other modes of delivery are, nonetheless, appropriate depending on the condition being treated. Aerosols are an example of an appropriate mode of delivery.

The compositions and pharmaceutical preparations may be administered in effective amounts. An effective amount, in general, means that amount necessary to achieve the purpose for which the active agent is applied. The effective amount will depend upon the mode of administration, the particular condition being treated, the severity of the condition, the needs of the patient, and the desired outcome. It will also depend upon, as discussed above, the stage of the condition, the age and physical condition of the subject, frequency of treatment and mode of treatment, the nature of concurrent therapy, if any, and like factors well known to the medical practitioner. If the active agent is a pharmaceutical agent, then the amount is that amount necessary to delay the onset of, slow the progression of, halt altogether the onset or progression of, or diagnose a particular condition being treated. In the case of a cosmetic agent, the effective amount will be that amount necessary to achieve the desired cosmetic result. In the case of a sunscreen agent, an effective amount will be that amount necessary to achieve suitable protection from the sun as is conventional.

Generally, doses of active compounds of the present invention would be from about 0.01 mg/kg per day to 1000 mg/kg per day. It is expected that doses ranging from 1-500 mg/kg, and preferably doses ranging from 1-100 mg/kg, and even more preferably doses ranging from 1-50 mg/kg, will be suitable. A variety of administration routes are available, although topical routes are preferred. The methods of the invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, topical, nasal or interdermal routes.

The active agents, the microparticles and the formulations in which they are provided can be in solid, semi-solid or liquid form. Solid forms include for example, powders, granules and flakes. Semi-solid forms include, for example, gels, creams, gelatins and ointments. Formulations for topical administration are known to those of ordinary skill in the art and, in most cases, are commercially available from suppliers such as Paddock

Laboratories and Gallipot. Information on topically active and inactive agents, and their commercial suppliers is available from various trade manuals, most particularly, Remington's Pharmaceutical Sciences, United States Pharmacopoeia (USP), National Formulary (NF), Merck Index, Physician's Desk Reference (PDR) and Chemical Abstracts.

The invention also involves kits. In general, the kits contain a compound of Formula I, Formula II or Formula III along with instructions for use of the particular compound. Compounds of Formula I, II or III are housed within containers, which may also contain catalysts, preservatives, buffers, vehicles, and the like, as is conventional. The package also may house instructions for using the materials according to the invention. Kits containing compounds of Formula II may also contain agents of the invention (e.g., those that are amine and/or thiol containing) in a separate container.

Referring to an exemplary kit in Figure 1, the kit is a package 10 comprising a housing 12 holding a first container 14, a second container 16 and a third container 18. As an example, a kit may be comprised of a first container which houses a bifunctional reactive compound of the invention (e.g., a compound of Formula II), either alone, or in a pharmaceutically acceptable carrier, or in a topically applied formation. The kit may also contain a second container which houses a microparticle composition comprising the agent. A third container may also be provided which contains, for example, a linking molecule for preparing the surface of the body tissue for application of the bifunctional reactive compounds and the microparticles. The various containers may also contain preservatives, buffers, vehicles, and the like, as is conventional. The kit also houses instructions for using the materials according to the invention, particularly for the topical administration of the linking molecules, compounds and microparticles. The instructions may be provided separately from the containers (e.g., on a sheet of paper enclosed in the kit) or on one of the containers (e.g., text on the outside surface of a container).

The agent may be a sunscreen agent. Examples of sunscreen agents include: p-aminobenzoate analogs such as 2-ethylhexyl-4-dimethylaminobenzoate (Padimate O); p-methoxy-2-ethyl-hexyl-cinnamate (Parsol 1789); oxybenzone (benzophenone-3); ethylhexylsalicylate; diphenylacrylate polyisobutylene; alkyl-$,$-diphenylacrylate and "-cyano-$,$-diphenylacrylate; 1-(4-aminophenyl)-2-morpholinylethanone; (1-(4-methoxylphenyl)-3-(4-tert-butyl-phenyl)-propan-1-3-dione; methyl anthranilate; octocrylene; Tretinoin "-hydroxyacid; diphenylacrylate polyisobutylene; 1-(4-aminophenyl)-2-morpholinylethanone; diphenylacrylate polyisobutylene; digalloyl trioleate; glyceryl

p-aminobenzoate; 4-(omega -dialkylaminoalkoxy)phenylmethylene)-1,3,3-trimethyl-2-oxabicyclo(2.2.2)octan-6-ones; 5-(arylmethylene)-1,3,3-trimethyl-2-oxabicyclo(2.2.2)octan-6-ones; melanin.

Further examples of sunscreen agents include: 3-benzylidene camphor; 4-methylbenzylidene camphor; allantoin PABA benzalphthalide; benzophenone; benzophenone-1; benzophenone-10; benzophenone-11; benzophenone-12; benzophenone-2; benzophenone-3; benzophenone-4; benzophenone-5; benzophenone-6; benzophenone-7; benzophenone-8; benzophenone-9; benzyl salicylate; benzylidene camphor sulfonic acid; bornelone; bumetrizole; butyl methoxydibenzoylmethane; camphor benzalkonium methosulfate; cinoxate; DEA-methoxycinnamate; diisopropyl methyl cinnamate; dimethyl PABA ethyl cetearyldimonium tosylate; drometrizole; ethyl cinnamate; ethyl dihydroxypropyl PABA; ethyl diisopropylcinnamate; ethyl methoxycinnamate; ethyl urocanate; etocrylene; glyceryl octanoate dimethoxycinnamate; glyceryl PABA; glycol salicylate; homosalate; isoamyl p-methoxycinnamate; isopropyl dibenzoylmethane; isopropyl methoxycinnamate; isopropylbenzyl salicylate; menthyl anthranilate; menthyl salicylate; n-ethyl-3-nitro PABA; octocrylene; octrizole; octyl dimethyl PABA; octyl methoxycinnamate; octyl salicylate; octyl triazone; PABA; PEG-25 PABA; phenylbenzimidazole sulfonic acid; polyacrylamidomethyl benzylidene camphor; potassium methoxycinnamate; potassium phenylbenzimidazole sulfonate; red petrolatum; sodium phenylbenzimidazole sulfonate; tea-phenylbenzimidazole sulfonate; tea-salicylate; terephthalylidene dicamphor sulfonic acid; tripaba panthenol; urocanic acid.

Other examples of sunscreen agents include: derivatives of para-amine benzoic acid (PABA); salicylates; cinnamates; benzophenones; camphors;4-aminobenzoic acid; N,N,N-trimethyl-4-(2-oxoborn-3-ylidenemethyl) anilinium methyl sulphate; homosalate (INN); oxybenzone (INN); 2-phenylbenzimidazole-5-sulphonic acid and its potassium, sodium and triethanolamine salts; 3,3'-(1,4-phenylenedimethylene) bis (7,7-dimethyl-2-oxobicyclo-[2.2.1] hept-1-ylmethanesulphonic acid) and its salts; 1-(4-tert-butylphenyl)-3-(4-methoxyphenyl) propane-1,3-dione; alpha-(2-oxoborn-3-ylidene) toluene-4-sulphonic acid and its salts; 2-cyano-3,3-diphenyl acrylic acid, 2-ethylhexyl ester (octocrylene); polymer of N-{(2 and 4)-[(2-oxoborn-3-ylidene)methyl] benzyl}acrylamide; octyl methoxycinnamate; ethoxylated ethyl-4-aminobenzoate (PEG-25 PABA); isopentyl-4-methoxycinnamate (isoamyl p-methoxycinnamate); 2,4,6-trianilino-(p-carbo-2ethylhexyl-l'-oxy)-1,3,5-triazine (octyl triazone); phenol 2-(2h-benzotriazol-2-yl)-4-methyl-6-(2-methyl-3-(1,3.3,3-tetramethyl-1-(trimethylsilyl)oxy)-disiloxanyl)propyl) (drometrizole trisiloxane); 3-(4'-methylbenzylidene)-d-1 camphor (4-methylbenzylidene camphor); 3-benzylidene camphor (3-benzylidene camphor); 2-ethylhexyl salicyclate (octyl-salicylate); 2-ethylhexyl-4-dimethyl-aminobenzoate; 2-hydroxy-4-methoxybenzo-phenone-5-sulphonic acid and sodium salt (sulisobenzone and sulisobenzone sodium); 4-isopropylbenzyl salicylate; cinnamic derivatives, such as, for example, 2-ethylhexyl p-methoxycinnamate; salicylic derivatives, such as, for example, 2-ethylhexyl salicylate; camphor derivatives, such as, for example, (4-methylbenzylidene)camphor or benzene-1,4-di(3-methylidene-10-camphorsulfonic) acid; benzimidazole derivatives, such as 2-phenylbenzimidazole-5-sulfonic acid; benzophenone derivatives, such as 2-hydroxy-4-methoxybenzophenone; dibenzoylmethane derivatives, such as 4-tert-butyl-4'-methoxydibenzoylmethane, or β,β-diphenylacrylate derivatives, such as 2-ethylhexyl α-cyano-β,β-diphenylacrylate; p-aminobenzoic acid, cinoxate, diethanolamine,

p-methoxycinnamate, digalloyl trioleate, dioxybenzone, ethyl 4-›bis›hydroxypropyl!aminobenzoate, 2-ethylhexyl 2-cyano-3,3-diphenylacrylate, ethylhexyl p-methoxycinnamate, 2-ethyhexyl salicylate, glyceryl aminobenzoate, homosalate (3,3,5-trimethylcyclohexylsalicylate), lawsone (2-hydroxy-1,4-naphthoquinone) with or without dihydroxyacetone, methyl anthranilate, oxybenzone, Padimate A, Padimate 0, 2-phenylbenzimidazole-5-sulfonic acid, triethanolamine salicylate, red petrolatum, and suisobenzone; titanium dioxide or zinc oxide.

The agent may also be a cosmetic agent. Examples of cosmetic components include: Vitamin C; Alpha -tocopherol (Vitamin E analog); Ammonium lauryl Sulfate; Cocamidopropyl Betaine; Lauramide DEA; Cocamide DEA; Methyl paraben; Propyl paraben; Butyl paraben; Salicylic acid; Propylene glycol; EDTA; BHT; BHA; TBHQ; DMDM hydantoin; Imidazolidinyl urea; Potassium sorbate; Sodium Benzoate; phenoxyethanol; Polysorbate 20 and 80; Sodium laurylether sulfate; Oleyl betaine; Tego betaine; Sorbitol; Glycerin monolaurate; Glycerol stearate.

The agent may also be a coloring agent for coloring hair or skin. A coloring agent is one which is able to change the color of skin, hair or nails. Color change may be effected through for example, a lightening or darkening of skin, hair or nails. Examples of coloring agents for hair include: 1,2,4-benzenetriacetate; 1,2,4-trihydroxybenzene; 1,3-bis-(2,4-diaminophenoxy)propane; 1,5-naphthalenediol; 1-naphthol; 2,3-naphthalenediol; 2,4-diamino-5-methylphenetol HCl; 2,4-diamino-5-methylphenoxyethanol HCl; 2,4-diaminodiphenylamine; 2,4-diaminophenol; 2,4-diaminophenol HCl; 2,4-diaminophenoxyethanol HCl; 2,6-bis(2-hydroxyethoxy)-3,5-pyridinediamine HCl; 2,6-diaminopyridine; 2,6-dimethoxy-3,5-pyridinediamine HCl; 2,7-naphthalenediol; 2-amino-3-hydroxypyridine; 2-amino-3-nitrophenol; 2-amino-4-hydroxyethylaminoanisole; 2-amino-4-hydroxyethylaminoanisole sulfate; 2-amino-6-chloro-4-nitrophenol; 2-aminomethyl-p-aminophenol HCl; 2-chloro-5-nitro-n-hydroxyethyl p-phenylenediamine; 2-chloro-6-ethylamino-4-nitrophenol; 2-chloro-p-phenylenediamine; 2-chloro-p-phenylenediamine sulfate; 2-hydroxyethyl picramic acid; 2-hydroxyethylamino-5-nitroanisole; 2-methoxymethyl-p-aminophenol HCl; 2-methyl-5-hydroxyethylaminophenol; 2-methylresorcinol; 2-nitro-5-glyceryl methylaniline; 2-nitro-n-hydroxyethyl-p-anisidine; 2-nitro-p-phenylenediamine; 3,4-diaminobenzoic acid; 3,4-methylenedioxyaniline; 3,4-methylenedioxyphenol; 3-methylamino-4-nitrophenoxyethanol; 3-nitro-4-aminophenoxyethanol; 3-nitro-p-cresol; 3-nitro-p-hydroxyethylaminophenol; 4,4-diaminodiphenylamine; 4,5-diamino-1-methylpyrazole HCl; 4,6-bis(2-hydroxyethoxy)-m-phenylenediamine HCl; 4-amino-2-hydroxytoluene; 4-amino-2-nitrodiphenylamine-2-carboxylic acid; 4-amino-3-nitrophenol; 4-amino-m-cresol; 4-chlororesorcinol; 4-hydroxyindole; 4-hydroxypropylamino-3-nitrophenol; 4-methoxytoluene-2,5-diamine HCl; 4-nitro-m-phenylenediamine; 4-nitro-o-phenylenediamine; 4-nitro-o-phenylenediamine HCl; 4-nitrophenyl aminoethylurea; 5-amino-2,6-dimethoxy-3-hydroxypyridine; 5-amino-6-chloro-o-cresol; 6-amino-m-cresol; 6-amino-o-cresol; 6-hydroxyindole; 6-methoxy-2,3-pyridinediamine HCl; 6-nitro-2,5-pyridinediamine; 6-nitro-o-toluidine; acacia catechu; acid black 1; acid black 52; acid blue 1; acid blue 3; acid blue 62; acid blue 74; acid blue 9; acid brown 13; acid green 1; acid green 25; acid green 50; acid orange 24; acid orange 3; acid orange 6; acid orange 7; acid red 14; acid red 18; acid red 27; acid red 33; acid red 35; acid red 51; acid red 52;

acid red 73; acid red 87; acid red 92; acid red 95; acid violet 43; acid violet 9; acid yellow 1; acid yellow 23; acid yellow 3; acid yellow 73 sodium salt; basic blue 26; basic blue 41; basic blue 6; basic blue 7; basic blue 9; basic blue 99; basic brown 16; basic brown 17; basic brown 4; basic green 1; basic red 2; basic red 22; basic red 76; basic violet 14; basic yellow 11; basic yellow 57; brilliant black 1; chromium hydroxide green; chromium oxide greens; curry red; dihydroxyindole; direct black 51; direct blue 86; direct red 23; direct red 80; direct red 81; direct violet 48; direct yellow 12; disperse black 9; disperse blue 1; disperse blue 3; disperse blue 7; disperse brown 1; disperse orange 3; disperse red 11; disperse red 15; disperse red 17; disperse violet 1; disperse violet 4; fast green FCF; HC blue No. 10; HC blue No. 11; HC blue No. 12; HC blue No. 2; HC blue No. 4; HC blue No. 5; HC blue No. 6; HC blue No. 7; HC blue No. 8; HC blue No. 9; HC brown No. 1; HC brown No. 2; HC green No. 1; HC orange No. 1; HC orange No. 2; HC orange No. 3; HC red No. 1; HC red No. 10; HC red No. 11; HC red No. 13; HC red No. 3; HC red No. 7; HC red No. 8; HC red No. 9; HC violet No. 1; HC violet No. 2; HC yellow No. 10; HC yellow No. 11; HC yellow No. 12; HC yellow No. 13; HC yellow No. 2; HC yellow No. 4; HC yellow No. 5; HC yellow No. 6; HC yellow No. 7; HC yellow No. 8; HC yellow No. 9; henna; hydroquinone; hydroxyanthraquinoneaminopropyl methyl morpholinium methosulfate; hydroxybenzomorpholine; hydroxyethyl-2,6-dinitro-p-anisidine; hydroxyethyl-2-nitro-p-toluidine; hydroxyethyl-3,4-methylenedioxyaniline HCl; hydroxyethyl-p-phenylenediamine sulfate; hydroxyethylaminomethyl-p-aminophenol HCl; hydroxypropyl bis(n-hydroxyethyl-p-phenylenediamine) HCl; lawsone; lead acetate; m-aminophenol; m-aminophenol HCl; m-aminophenol sulfate; m-phenylenediamine; m-phenylenediamine sulfate; N,N-bis(2-hydroxyethyl)-p-phenylenediamine sulfate; N,N-diethyl-m-aminophenol; N,N-diethyl-m-aminophenol sulfate; N,N-dimethyl 2,6-pyridinediamine HCl; N,N-dimethyl-p-phenylenediamine; N,N-dimethyl-p-phenylenediamine sulfate; N,N-bis(2-hydroxyethyl)-2-nitro-p-phenylenediamine; N,N-dimethyl-n-hydroxyethyl-3-nitro-p-phenylendiamine; n-ethyl-3-nitro PABA; n-methoxyethyl-p-phenylenediamine HCl; n-methyl-3-nitro-p-phenylenediamine; n-phenyl-p-phenylenediamine; n-phenyl-p-phenylenediamine HCl; n-phenyl-p-phenylenediamine sulfate; o-aminophenol; p-aminophenol; p-aminophenol HCl; p-aminophenol sulfate; p-methylaminophenol; p-methylaminophenol sulfate; p-phenylenediamine; p-phenylenediamine HCl; p-phenylenediamine sulfate; phenyl methyl pyrazolone; phloroglucinol; picramic acid; pigment blue 15; pigment green 7; pigment red 112; pigment red 172 aluminum lake; pigment red 4; pigment red 48; pigment red 5; pigment red 57; pigment red 57:1; pigment red 63:1; pigment red 64:1; pigment red 83; pigment red 90:1 aluminum lake; pigment violet 19; pigment violet 23; pigment yellow 12; pigment yellow 13; pigment yellow 73; ponceau sx; resorcinol; silver nitrate; sodium picramate; solvent black 3; solvent green 3; solvent green 7; solvent orange 1; solvent red 1; solvent red 23; solvent red 3; solvent red 43; solvent red 48; solvent red 72; solvent red 73; solvent violet 13; solvent yellow 29; solvent yellow 33; solvent yellow 44; sunset yellow; thymol; toluene-2,5-diamine; toluene-2,5-diamine sulfate; toluene-3,4-diamine; ultramarines; VAT red 1; m- and p-phenylenediamines, their N-substituted derivatives and their salts; N-substituted derivatives of o-phenylenediamines; methylphenylenediamines, their N-substituted derivatives and their salts; diaminophenols; hydroquinone; alpha-naphthol; lead acetate.

Coloring agents also include bleaching agents such as ammonium persulfate; hydroquinone and strontium dioxide.

Other examples of coloring agents are cosmetic colorants which include: acid red 195; aluminum stearate; anthocyanins; beta vulgaris; beta vulgaris; bismuth oxychloride; bromocresol green; bromothymol blue; calcium stearate; capsanthin/capsorubin caramel; CI 10006; CI 10020; CI 10316; CI 10316; CI 11680; CI 11710; CI 11725; CI 11920; CI 12010; CI 12085; CI 12120; CI 12150; CI 12370; CI 12420; CI 12480; CI 12490; CI 12700; CI 13015; CI 14270; CI 14700; CI 14700; CI 14720; CI 14815; CI 15510; CI 15510; CI 15525; CI 15580; CI 15620; CI 15630; CI 15800; CI 15850; CI 15850; CI 15850; CI 15850; CI 15850; CI 15850; CI 15850; CI 15850; CI 15850; CI 15850; CI 15850; CI 15865; CI 15865; CI 15880; CI 15980; CI 15985; CI 15985; CI 16035; CI 16185; CI 16185; CI 16230; CI 16255; CI 16290; CI 17200; CI 17200; CI 18050; CI 18130; CI 18690; CI 18736; CI 18820; CI 18965; CI 19140; CI 19140; CI 19140; CI 20040; CI 20170; CI 20470; CI 21100; CI 21108; CI 21230; CI 24790; CI 26100; CI 27290; CI 27755; CI 28440; CI 40215; CI 40800; CI 40820; CI 40825; CI 40850; CI 42045; CI 42051; CI 42053; CI 42080; CI 42090; CI 42090; CI 42090; CI 42100; CI 42170; CI 42510; CI 42520; CI 42735; CI 44045; CI 44090; CI 45100; CI 45190; CI 45220; CI 45350; CI 45350; CI 45370; CI 45370; CI 45370; CI 45370; CI 45380; CI 45380; CI 45380; CI 45380; CI 45396; CI 45405; CI 45410; CI 45410; CI 45410; CI 45410; CI 45410; CI 45410; CI 45410; CI 45410; CI 45425; CI 45425; CI 45425; CI 45430; CI 45430; CI 47000; CI 47005; CI 47005; CI 50325; CI 50420; CI 51319; CI 58000; CI 59040; CI 60724; CI 60725; CI 60730; CI 61565; CI 61570; CI 61585; CI 62045; CI 69800; CI 69825; CI 71105; CI 73000; CI 73015; CI 73015; CI 73360; CI 73385; CI 73900; CI 73915; CI 74100; CI 74160; CI 74180; CI 74260; CI 75100; CI 75120; CI 75125; CI 75130; CI 75135; CI 75170; CI 75300; CI 75470; CI 75810; CI 75810; CI 75810; CI 75810; CI 77000; CI 77002; CI 77004; CI 77004; CI 77004; CI 77007; CI 77015; CI 77120; CI 77163; CI 77220; CI 77231; CI 77266; CI 77267; CI 77268:1; CI 77288; CI 77289; CI 77346; CI 77400; CI 77480; CI 77489; CI 77491; CI 77492; CI 77499; CI 77510; CI 77713; CI 77742; CI 77745; CI 77820; CI 77891; CI 77947; lactoflavin; magnesium stearate; riboflavin and zinc stearate.

The agent may also be a moisturizing agent. A moisturizing agent is an agent which softens and smoothens skin and in some instances hair. Some moisturizing agents are also humectants in that they are able to hold and retain moisture. Emollient agents can be moisturing agents. Moisturizing agents can be used soften skin prior to abrasive events such as shaving. In these latter embodiments, the composition of the invention comprising a moisturizing agent can be supplied in a shaving gel or creme. Examples of moisturizing agents include: proteoglycans and glycosaminoglycans including hyaluronic acid, crosslinked hyaluronic acid, derivatized hyaluronic acid, chondroitin sulfate; mono- and poly-hydroxyl containing chemicals such as glycerin, sorbitol; pyrrolidine carboxylic acid; proteins such as hydrolyzed animal and vegetable protein, collagens, derivatized collagens, elastins; allantoin; polymer skin conditioning agents; polyols such as glycerol; chitosans; derivatized chitosans; and polyglutamine.

Other examples of moisturizing agents include D,L-panthenol, D-panthenol, vitamin A palmitate, vitamin E acetate, methylsilanetriol mannuronate, natural oils such as tallow oil, macadamia nut oil, borage oil, evening primrose oil, kukui nut oil, rice bran oil, tea tree oil, a medium chain fatty acid ester of glycerol, such as

glycerol triheptanoate, glyceryl trioctanoate, glycerol trioctanoate, mineral water, silicones, silicone derivatives; allantoin; dipotassium glycyrrhizinate; stearyl glycyrrhizinate; squalane NF; squalane EX; cetyl ester wax; orange roughy oil; hydrogenated phospholipids; hydrocarbon oils and waxes, such as mineral oil, polyethylene and paraffin; triglyceride esters, such as olive oil, avocado oil, and squalene; lanolin and derivatives; ether-esters, such as fatty acid esters of ethoxylated fatty alcohols; and fatty acids having 10 to 20 carbon atoms, such as lauric, myristic, oleyl, and stearate.

Emollients useful in the invention as moisturizers include: acetamidoethoxybutyl trimonium chloride; acetyl trioctyl citrate; acetylated castor oil; acetylated cetyl hydroxyprolinate; acetylated glycol stearate; acetylated hydrogenated cottonseed glyceride; acetylated hydrogenated lanolin; acetylated hydrogenated lard glyceride; acetylated hydrogenated tallow glyceride; acetylated hydrogenated tallow glycerides; acetylated hydrogenated vegetable glyceride; acetylated lanolin; acetylated lanolin alcohol; acetylated lanolin ricinoleate; acetylated lard glyceride; acetylated palm kernel glycerides; acetylated sucrose distearate; adeps bovis; adeps suillus; aleurites moluccana; allyl caproate;almond oil peg-6 esters; aloe barbadensis; althea officinalis; aluminum hydroxide; aluminum stearates; aluminum tristearate; amodimethicone/dimethicone copolyol; amp-isostearoyl hydrolyzed collagen; anacardium occidentale; apple peel wax; apricot kernel oil PEG-6 esters; arachidonic acid; arachidyl alcohol; arachidyl behenate; arachidyl glycol isostearate; arachidyl propionate; arachis hypogaea; arctium lappa; avena sativa; avocado oil PEG-11 esters; bassia latifolia; batyl alcohol; batyl isostearate; batyl stearate; bayberry wax; behenoxy dimethicone; behenyl/isostearyl beeswax; behenyl alcohol; behenyl behenate; behenyl erucate; behenyl isostearate; benzyl laurate; bis-diglyceryl/caprylate/caprate/isostearate/hydroxystearate adipate; bis-diglyceryl caprylate/caprate/isostearate/stearate/hydroxystearate adipate; bisphenylhexamethicone; borago officinalis; borago officinalis; brassica botrytis; brassica oleifera; brassica oleifera; brevoortia; bubulum; butyl acetyl ricinoleate; butyl isostearate; butyl myristate; butyl oleate; butyl stearate; butylene glycol dicaprylate/dicaprate; butylene glycol montanate; butyloctyl beeswax; butyloctyl oleate; butyrospermum parkii; butyroyl trihexyl citrate; butyrum; buxus chinensis; C10-18 triglycerides; C11-15 pareth-12 stearate; C11-15 pareth-3 oleate; C11-15 pareth-3 stearate; C12-13 alcohols; C12-13 alkyl lactate; C12-13 alkyl octanoate; C12-15 alcohols; C12-15 alkyl benzoate; C12-15 alkyl lactate; C12-15 alkyl octanoate; C12-15 pareth-12 oleate; C12-16 alcohols; C12-18 acid triglyceride; C13-14 isoparaffin; C15-18 glycol; C18-28 alkyl acetate; C18-36 acid glycol ester; C18-36 acid triglyceride; C18-38 alkyl beeswax; C18-70 isoparaffin; C20-40 alkyl behenate; C20-40 isoparaffin; C24-28 alkyl methicone; C30-45 alkyl methicone; C9-11 alcohols; Calendula officinalis; camelina sativa; cananga odorata; candelilla cera; canola; capryl glycol; caprylic/capric/diglyceryl succinate; caprylic/capric/lauric triglyceride; caprylic/capric/linoleic triglyceride; caprylic/capric/myristic/stearic triglyceride; caprylic/capric/stearic triglyceride; caprylic/capric glycerides; caprylic/capric triglyceride; carnauba; carthamus tinctorius; carthamus tinctorius; cera alba; ceratonia siliqua; ceratonia siliqua; cetearyl alcohol; cetearyl behenate; cetearyl candelillate; cetearyl isononanoate; cetearyl octanoate; cetearyl palmitate; cetyl acetate; cetyl acetyl ricinoleate; cetyl alcohol; cetyl C12-15-pareth-9 carboxylate; cetyl caprylate; cetyl dimethicone; cetyl esters; cetyl glycol; cetyl glycol isostearate; cetyl isononanoate; cetyl lactate; cetyl laurate; cetyl myristate; cetyl octanoate; cetyl oleate; cetyl palmitate; cetyl ricinoleate; cetyl stearate; cetylarachidol;

chamomilla recutita; chimyl isostearate; cholesterol; cholesteryl hydroxystearate; cholesteryl isostearate; cholesteryl macadamiate; cholesteryl nonanoate; cholesteryl stearate; cistus ladaniferus; cocaminobutyric acid; cocaminopropionic acid; coco-caprylate/caprate; coco-rapeseedate; cocoglycerides; coconut acid; coconut alcohol; cocos nucifera; cocoyl glutamic acid; coenzyme a; corn acid; corn oil PEG-6 esters; corn oil PEG-8 esters; corylus americana; corylus avellana; cottonseed acid; cottonseed glyceride; cucumis sativus; cucurbita pepo; curcuma zedoaria; cyatheaceae; cyclomethicone; dalea spinosa; daucus carota; decyl alcohol; decyl isostearate; decyl myristate; decyl oleate; decyl succinate; decyltetradecanol; di-C12-13 alkyl malate; di-C12-13 alkyl tartrate; di-C12-15 alkyl adipate; dibutyl adipate; dibutyl sebacate; dicapryl adipate; dicaprylyl maleate; dicetyl adipate; dicocamine; dicocodimethylamine dilinoleate; dicocoyl pentaerythrityl distearyl citrate; didecene; diethyl palmitoyl aspartate; diethyl sebacate; diethyl succinate; diethylene glycol dibenzoate; diethylene glycol diisononanoate; diethylene glycol dioctanoate; diethylene glycol dioctanoate/diisononanoate; dihexyl adipate; dihydroabietyl behenate; dihydrocholesterol; dihydrocholesteryl octyldecanoate; dihydrogenated tallow phthalate; dihydrophytosteryl octyldecanoate; dihydroxyethyl soyamine dioleate; dihydroxyethylamino hydroxypropyl oleate; diisobutyl adipate; diisocetyl adipate; diisodecyl adipate; diisononyl adipate; diisopropyl adipate; diisopropyl dimer dilinoleate; diisopropyl sebacate; diisostearyl adipate; diisostearyl dimer dilinoleate; diisostearyl fumarate; diisostearyl glutarate; diisostearyl malate; dilaureth-7 citrate; dilauryl citrate; dilinoleic acid; dimethicone; dimethicone copolyol; imethicone copolyol almondate; dimethicone copolyol avocadoate; dimethicone copolyol beeswax; dimethicone copolyol cocoa butterate; dimethicone copolyol olivate; dimethicone copolyol phthalate; dimethicone copolyol shea butterate; dimethicone propylethylenediamine behenate; dimethiconol; dimethiconol hydroxystearate; dimethiconol isostearate; dimethiconol stearate; dimethyl adipate; dimethyl lauramine dimer dilinoleate; dimethyl lauramine isostearate; dimethyl maleate; dimethyl succinate; dimethyl tallowamine; dioctyl adipate; dioctyl dimer dilinoleate; dioctyl malate; dioctyl sebacate; dioctyl succinate; dioctylcyclohexane; dioctyldodecyl dimer dilinoleate; dipentaerythrityl hexaheptanoate/hexacaprylate/hexacaprate dipropyl adipate; dipropylene glycol dibenzoate; distearyldimethylamine dilinoleate; ditridecyl adipate; ditridecyl dimer dilinoleate; dodecyltetradecanol; dromiceius; elaeis guineensis; elaeis guineensis; epoxidized soybean oil; erucyl arachidate; erucyl erucate; erucyl oleate; ethiodized oil; ethyl arachidonate; ethyl avocadate; ethyl ester of hydrolyzed animal protein; ethyl isostearate; ethyl laurate; ethyl linoleate; ethyl linolenate; ethyl minkate; ethyl morrhuate; ethyl myristate; ethyl oleate; ethyl olivate; ethyl palmitate; ethyl pelargonate; ethyl persate; ethyl stearate; fish glycerides; gadi iecur; glycereth-7 triacetate; glycerin/oxybutylene copolymer stearyl ether; glyceryl/sorbitol oleate/hydroxystearate; glyceryl abietate; glyceryl adipate; glyceryl arachidate; glyceryl arachidonate; glyceryl behenate; glyceryl caprate; glyceryl caprylate; glyceryl caprylate/caprate; glyceryl cocoate; glyceryl diarachidate; glyceryl dibehenate; glyceryl dierucate; glyceryl dihydroxystearate; glyceryl diisopalmitate; glyceryl diisostearate; glyceryl dilaurate; glyceryl dilinoleate; glyceryl dimyristate; glyceryl dioleate; glyceryl dipalmitate; glyceryl dipalmitoleate; glyceryl diricinoleate; glyceryl distearate;glyceryl erucate; glyceryl hydroxystearate; glyceryl isostearate; glyceryl lanolate; glyceryl laurate; glyceryl laurate/oleate; glyceryl linoleate; glyceryl linolenate; glyceryl myristate;glyceryl octanoate/stearate/adipate; glyceryl oleate; glyceryl palmitate; glyceryl palmitate/stearate; glyceryl palmitate lactate; glyceryl ricinoleate; glyceryl sesquioleate; glyceryl stearate;

glyceryl stearate citrate; glyceryl stearate diacetate; glyceryl stearate lactate; glyceryl triacetyl hydroxystearate; glyceryl triacetyl ricinoleate; glycine soja; glycine soja; glycol/butylene glycol montanate; glycol cetearate; glycol dibehenate; glycol dilaurate; glycol dioctanoate; glycol dioleate; glycol distearate; glycol ditallowate; glycol hydroxystearate; glycol oleate; glycol ricinoleate; glycol stearate; glycosaminoglycans; glycosphingolipids; gossypium; helianthus annus; helianthus annuus; heptylundecanol; hexadecyl methicone; hexamethyldisiloxane; hexanediol distearate; hexyl isostearate; hexyl laurate; hexyldecyl oleate; hordeum vulgare; hordeum vulgare; hydrogenated butylene/ethylene/styrene copolymer; hydrogenated C12-18 triglycerides; hydrogenated c6-14 olefin polymers; hydrogenated castor oil; hydrogenated castor oil laurate; hydrogenated coco-glycerides; hydrogenated coconut acid; hydrogenated coconut oil; hydrogenated cottonseed glyceride; hydrogenated cottonseed oil; hydrogenated ethylene/propylene/styrene copolymer; hydrogenated fish oil; hydrogenated jojoba oil; hydrogenated jojoba wax; hydrogenated lanolin; hydrogenated lard; hydrogenated menhaden oil; hydrogenated mink oil; hydrogenated olive oil unsaponifiables; hydrogenated orange roughy oil; hydrogenated palm/palm kernel oil PEG-6 esters; hydrogenated palm glyceride; hydrogenated palm glycerides; hydrogenated palm kernel glycerides; hydrogenated palm kernel oil; hydrogenated palm oil; hydrogenated peanut oil; hydrogenated polyisobutene; hydrogenated rapeseed oil; hydrogenated shark liver oil; hydrogenated soy glyceride; hydrogenated soybean glycerides; hydrogenated soybean oil; hydrogenated tallow; hydrogenated tallow acid; hydrogenated tallow alcohol; hydrogenated tallow glyceride; hydrogenated tallow glyceride citrate; hydrogenated tallow glyceride lactate; hydrogenated tallow glycerides; hydrogenated tallow glycerides citrate; hydrogenated vegetable glyceride; hydrogenated vegetable glycerides; hydrogenated vegetable glycerides phosphate; hydrogenated vegetable oil; hydrolyzed collagen; hydroxylated lanolin; hydroxylated milk glycerides; hydroxyoctacosanyl hydroxystearate; hyptis suaveolens; isatis tinctoria; isoamyl laurate; isobutyl myristate; isobutyl palmitate; isobutyl pelargonate; isobutyl stearate; isobutyl tallowate; isobutylated lanolin oil; isocetyl alcohol; isocetyl behenate; isocetyl isodecanoate; isocetyl linoleoyl stearate; isocetyl myristate; isocetyl palmitate; isocetyl salicylate; isocetyl stearate; isocetyl stearoyl stearate; isodeceth-2 cocoate; isodecyl citrate; isodecyl cocoate; isodecyl hydroxystearate; isodecyl isononanoate; isodecyl laurate; isodecyl myristate; isodecyl neopentanoate; isodecyl octanoate; isodecyl oleate; isodecyl palmitate; isodecyl stearate; isododecane; isododecene; isoeicosane; isohexadecane; isohexyl laurate; isohexyl neopentanoate; isohexyl palmitate; isolauryl behenate; isomerized jojoba oil; isononyl isononanoate; isopropyl arachidate; isopropyl avocadate; isopropyl behenate; isopropyl C12-15-pareth-9 carboxylate; isopropyl hydroxystearate; isopropyl isostearate; isopropyl lanolate; isopropyl laurate; isopropyl linoleate; isopropyl myristate; isopropyl oleate; isopropyl palmitate; isopropyl PPG-2-isodeceth-7 carboxylate; isopropyl ricinoleate; isopropyl stearate; isopropyl tallowate; isopropyl titanium triisostearate; isostearyl alcohol; isostearyl avocadate; isostearyl behenate; isostearyl benzoate; isostearyl erucate; isostearyl glyceryl pentaerythrityl ether; isostearyl isononanoate; isostearyl isostearate; isostearyl lactate; isostearyl myristate; isostearyl neopentanoate; isostearyl octanoate; isostearyl palmitate; isostearyl stearoyl stearate; isotridecyl isononanoate; isotridecyl myristate; jojoba alcohol; jojoba wax; juglans regia; lactis lipida; laneth-10 acetate; laneth-9 acetate; lanolin; lanolin; lanolin acid; lanolin alcohol; lanolin cera; lanolin linoleate; lanolin ricinoleate; lanosterol; lard glycerides; laureth-2 acetate; laureth-2 benzoate; laureth-2 octanoate; lauric/palmitic/oleic triglyceride; lauryl alcohol; lauryl behenate; lauryl cocoate;

lauryl glycol; lauryl isostearate; lauryl lactate; lauryl myristate; lauryl oleate; lauryl palmitate; lauryl stearate; lauryldimonium hydroxypropyl hydrolyzed collagen; laurylmethicone copolyol; lavandula hybrida; lecithin; lesquerella fendleri; limnanthes alba; linoleic acid; linolenic acid; linoleyl lactate; linseed acid; linum usitatissimum; macadamia ternifolia; maleated soybean oil; mangifera indica; mango seed oil PEG-70 esters; MEL; methicone; methyl acetyl ricinoleate; methyl caproate; methyl caprylate; methyl caprylate/caprate; methyl cocoate; methyl dehydroabietate; methyl gluceth-20 benzoate; methyl glucose dioleate; methyl glucose laurate; methyl glucose sesquicaprylate/sesquicaprate; methyl glucose sesquicocoate; methyl glucose sesquiisostearate; methyl glucose sesquilaurate; methyl glucose sesquioleate; methyl glucose sesquistearate; methyl hydroxystearate; methyl laurate; methyl linoleate; methyl myristate; methyl oleate; methyl palmitate; methyl pelargonate; methyl ricinoleate; methyl stearate; mink oil PEG-13 esters; moringa pterygosperma; mortierella isabellina; musa sapientum; mustela; mustela; myreth-2 myristate; myreth-3 caprate; myreth-3 laurate; myreth-3 myristate; myreth-3 octanoate; myreth-3 palmitate; myristoyl hydrolyzed collagen; myristyl alcohol; myristyl isostearate; myristyl lactate; myristyl lignocerate; myristyl myristate; myristyl neopentanoate; myristyl octanoate; myristyl propionate; myristyl stearate; neopentyl glycol dicaprate; neopentyl glycol dicaprylate/dicaprate; neopentyl glycol dicaprylate/dipelargonate/dicaprate; neopentyl glycol dioctanoate; nonyl acetate; octacosanyl glycol; octacosanyl glycol isostearate; octyl acetoxystearate; octyl cocoate; octyl hydroxystearate; octyl isononanoate; octyl isopalmitate; octyl isostearate; octyl laurate; octyl myristate; octyl neopentanoate; octyl octanoate; octyl oleate; octyl palmitate; octyl pelargonate; octyl stearate; octyldecanol; octyldodecanol; octyldodecyl behenate; octyldodecyl benzoate; octyldodecyl erucate; octyldodecyl lactate; octyldodecyl myristate; octyldodecyl neodecanoate; octyldodecyl neopentanoate; octyldodecyl octanoate; octyldodecyl oleate; octyldodecyl ricinoleate; octyldodecyl stearate; octyldodecyl stearoyl stearate; oenothera biennis; olea europaea; olea europaea; oleic/linoleic triglyceride; oleic/palmitic/lauric/myristic/linoleic triglyceride; oleic acid; oleostearine; oleoyl hydrolyzed collagen; oleyl acetate; oleyl alcohol; oleyl arachidate; oleyl erucate; oleyl lactate; oleyl lanolate; oleyl linoleate; oleyl myristate; oleyl oleate; oleyl stearate; olive oil PEG-10 esters; olive oil PEG-6 esters; olus; omental lipids; orange peel wax; orbignya oleifera; oryza sativa; oryza sativa; ovum; ozonized jojoba oil; palm glyceride; palm glycerides; palm kernel acid; palm kernel alcohol; palm kernel glycerides; palm kernel wax; palmitic acid; palmitoyl hydrolyzed collagen; pantethine; papaver orientale; paraffin; paraffinum liquidum; PCA glyceryl oleate; peanut oil PEG-6 esters; PEG/PPG-125/30 copolymer; PEG/PPG-35/9 copolymer; PEG-10 coconut oil esters; PEG-10 hydrogenated lanolin; PEG-10 lanolin; PEG-10 polyglyceryl-2 laurate; PEG-11 castor oil; PEG-2 milk solids; PEG-20 hydrogenated lanolin; PEG-20 methyl glucose distearate; PEG-200 hydrogenated glyceryl palmate; PEG-4 proline linoleate; PEG-4 proline linolenate; PEG-5 glyceryl triisostearate; PEG-5 hydrogenated lanolin; PEG-5 pentaerythrityl ether; PEG-5 tricetyl citrate; PEG-5 tridecyl citrate; PEG-5 trilauryl citrate; PEG-5 trimyristyl citrate; PEG-5 tristearyl citrate; PEG-75 lanolin; PEG-8 hydrogenated fish glycerides; PEG-8 linoleate; PEG-8 linolenate; pellis lipida; pentadecyl alcohol; pentadesma butyracea; pentadoxynol-200; pentaerythrityl dioleate; pentaerythrityl isostearate/caprate/caprylate/adipate; pentaerythrityl stearate; pentaerythrityl stearate/caprate/caprylate adipate; pentaerythrityl tetraabietate; pentaerythrityl tetraacetate; pentaerythrityl tetrabehenate; pentaerythrityl tetrabenzoate; pentaerythrityl tetracaprylate/caprate; pentaerythrityl tetracocoate; pentaerythrityl

tetraisononanoate; pentaerythrityl tetraisostearate; pentaerythrityl tetralaurate; pentaerythrityl tetramyristate; pentaerythrityl tetraoctanoate; pentaerythrityl tetraoleate; pentaerythrityl tetrapelargonate; pentaerythrityl tetrastearate; pentaerythrityl trioleate; pentahydrosqualene; perfluoropolymethylisopropyl ether; persea gratissima; persea gratissima; petrolatum; petroleum hydrocarbon; phenyl dimethicone; phenyl methicone; phenyl trimethicone; phosphatidylcholine; pimenta acris; piscum iecur; pistacia vera; placental lipids; polyglyceryl-4 cocoate; polygonum aviculare; polyisoprene; polypentene; polyquaternium-2; polysilicone-3; polysilicone-4; polysilicone-5; PPG-1 trideceth-6; PPG-1-ceteth-1; PPG-1-ceteth-10; PPG-1-ceteth-20; PPG-1-ceteth-5; PPG-10 butanediol; PPG-10 cetyl ether phosphate; PPG-10 jojoba acid; PPG-10 jojoba alcohol; PPG-10 methyl glucose ether; PPG-10 oleyl ether; PPG-11 stearyl ether; PPG-12; PPG-12/SMDI copolymer; PPG-12 butyl ether; PPG-12-PEG-50 lanolin; PPG-12-PEG-65 lanolin oil; PPG-15; PPG-15 stearyl ether; PPG-15 stearyl ether benzoate; PPG-17; PPG-17 butyl ether; PPG-17 dioleate; PPG-2 butyl ether; PPG-2 hydrogenated tallowamine; PPG-2 isostearate; PPG-2 lanolin alcohol ether; PPG-2 myristyl ether propionate; PPG-2-buteth-2; PPG-2-ceteth-1; PPG-2-ceteth-5; PPG-20; PPG-20 butyl ether; PPG-20 lanolin alcohol ether; PPG-20 methyl glucose ether acetate; PPG-20 oleyl ether; PPG-23 oleyl ether; PPG-23-steareth-34; PPG-25 butyl ether phosphate; PPG-26; PPG-26 butyl ether; PPG-26 oleate; PPG-3 myristyl ether; PPG-3-deceth-2 carboxylic acid; PPG-3-ISODECETH-1; PPG-30; PPG-30 cetyl ether; PPG-30 isocetyl ether; PPG-30 lanolin alcohol ether; PPG-30 oleyl ether; PPG-34; PPG-36 oleate; PPG-36-buteth-36; PPG-37 oleyl ether; PPG-4 jojoba acid; PPG-4 jojoba alcohol; PPG-4 laureth-2; PPG-4 laureth-7; PPG-4 lauryl ether; PPG-4 myristyl ether; PPG-4-buteth-4; PPG-4-ceteth-20; PPG-4-deceth-4; PPG-40-PEG-60 lanolin oil; PPG-5 lanolin alcohol ether; PPG-5 lanolin wax; PPG-5 lanolin wax glyceride; PPG-5 pentaerythrityl ether; PPG-5-buteth-5; PPG-5-laureth-5; PPG-50 oleyl ether; PPG-52 butyl ether; PPG-6-deceth-4; PPG-6-deceth-9; PPG-6-laureth-3; PPG-6-sorbeth-245; PPG-6-sorbeth-500; PPG-68-PEG-10 trimethylolpropane; PPG-7/succinic acid copolymer; PPG-7 lauryl ether; PPG-8 deceth-6; PPG-8 polyglyceryl-2 ether; PPG-9; PPG-9 diglyceryl ether; PPG-9 laurate; PPG-9-steareth-3; pristane; propylene glycol behenate; propylene glycol capreth-4; propylene glycol caprylate; propylene glycol ceteth-3 acetate; propylene glycol ceteth-3 propionate; propylene glycol citrate; propylene glycol cocoate; propylene glycol dicaprate; propylene glycol dicaproate; propylene glycol dicaprylate; propylene glycol dicaprylate/dicaprate; propylene glycol dicocoate; propylene glycol diisostearate; propylene glycol dilaurate; propylene glycol dioctanoate; propylene glycol dioleate; propylene glycol dipelargonate; propylene glycol distearate; propylene glycol hydroxystearate; propylene glycol isoceteth-3 acetate; propylene glycol isostearate; propylene glycol laurate; propylene glycol linoleate; propylene glycol linolenate; propylene glycol myristate; propylene glycol myristyl ether; propylene glycol myristyl ether acetate; propylene glycol oleate; propylene glycol oleth-5; propylene glycol ricinoleate; propylene glycol soyate; propylene glycol stearate; prunus armeniaca; prunus armeniaca; prunus avium; prunus dulcis; prunus persica; rapeseed glyceride; rapeseed glycerides; red petrolatum; rhus succedanea; ricinoleic acid; ricinus communis; rosa canina; rosa moschata; safflower glyceride; salmo; salvia hispanica; sesamum indicum; sesamum indicum; shellac; shellac cera; shorea stenoptera; silica dimethyl silylate; silica silylate; simethicone; sorbitan distearate; soy acid; sphingolipids; squalane; squalene; squali iecur; stearoxy dimethicone; stearoxymethicone/dimethicone copolymer; stearoxytrimethylsilane; stearyl/aminopropyl methicone copolymer; stearyl acetate; stearyl alcohol;

stearyl behenate; stearyl benzoate; stearyl caprylate; stearyl citrate; stearyl dimethicone; stearyl erucate; stearyl glycol; stearyl glycol isostearate; stearyl heptanoate; stearyl lactate; stearyl linoleate; stearyl methicone; stearyl octanoate; stearyl stearate; stearyl stearoyl stearate; sucrose distearate; sulfurized jojoba oil; sunflower seed oil glyceride; sunflower seed oil glycerides; synthetic candelilla wax; synthetic carnauba; synthetic japan wax; synthetic jojoba oil; synthetic wax; tall oil acid; tall oil glycerides; tall oil sterol; tallol; tallow acid; tallow alcohol; tallow glyceride; tallow glycerides; taraktogenos kurzii; tetrabutoxypropyl trisiloxane; tetradecyleicosanol; tetradecyleicosyl stearate; tetradecyloctadecanol; tetramethyl tetraphenyl trisiloxane; theobroma cacao; tri-C12-13 alkyl citrate; triarachidin; tribehenin; tricaprin; tricaprylin; tricaprylyl citrate; tridecyl alcohol; tridecyl behenate; tridecyl cocoate; tridecyl erucate; tridecyl isononanoate; tridecyl myristate; tridecyl neopentanoate; tridecyl octanoate; tridecyl stearate; tridecyl stearoyl stearate; tridecyl trimellitate; trierucin; triheptylundecanoin; trihydroxymethoxystearin; trihydroxystearin; triisocetyl citrate; triisononanoin; triisopalmitin; triisopropyl trilinoleate; triisostearin; triisostearin PEG-6 esters; triisostearyl citrate; triisostearyl trilinoleate; trilaurin; trilauryl citrate; trilinoleic acid; trilinolein; trilinolenin; trimethyl pentaphenyl trisiloxane; trimethylolpropane tricaprylate/tricaprate; trimethylolpropane tricocoate; trimethylolpropane triisostearate; trimethylolpropane trilaurate; trimethylolpropane trioctanoate; trimethylolpropane tristearate; trimethylsiloxysilicate; trimethylsilylamodimethicone; trimyristin; trioctanoin; trioctyldodecyl citrate; triolein; triolein PEG-6 esters; trioleyl phosphate; tripalmitin; tripalmitolein; triphenyl trimethicone; tripropylene glycol citrate; triricinolein; tris(tributoxysiloxy)methylsilane; trisebacin; tristearin; tristearyl citrate; triticum vulgare; triticum vulgare; triundecanoin; undecylpentadecanol; vegetable glycerides phosphate; vitis vinifera; wheat germ acid; wheat germ glycerides; zea mays.

Humectants useful in the invention as moisturizing agents include: 1,2,6-hexanetriol; acetamide MEA; aluminum hydroxide; arachidyl glycol; arginine PCA; butoxypropanol; butylene glycol; butyloctanol; capryl glycol; carboxymethyl chitosan succinamide; chitosan PCA; copper acetyl tyrosinate methylsilanol; copper PCA; copper PCA methylsilanol; cyclomethicone; diglycerin; dimethicone copolyol acetate; dimethicone copolyol adipate; dimethicone copolyol behenate; dimethicone copolyol butyl ether; dimethicone copolyol hydroxystearate; dimethicone copolyol isostearate; dimethicone copolyol laurate; dimethicone copolyol methyl ether; dimethicone copolyol phosphate; dimethicone copolyol stearate; dimethicone copolyolamine; dimethicone silylate; dimethyl imidazolidinone; dimethylsilanol hyaluronate; dipotassium glycyrrhizate; erythritol; ethoxydiglycol; fructose; glucamine; gluconic acid; glucose; glucose glutamate; glucuronic acid; glutamic acid; glutamic acid; glycereth-12; glycereth-20; glycereth-26; glycereth-7; glycerin; glycogen; glycyrrhetinyl stearate; glycyrrhizic acid; heilmoor clay; hexacosyl glycol; hexanediol beeswax; hexanetriol beeswax; hexyldecanol; histidine; histidine; hyaluronic acid; hydrogenated honey; hydrogenated starch hydrolysate; hydrolyzed collagen; hydrolyzed elastin; hydrolyzed glycosaminoglycans; hydrolyzed keratin; hydrolyzed silk; hydrolyzed soy protein; hydrolyzed wheat protein/dimethicone copolyol phosphate copolymer; hydroxyethyl sorbitol; inositol; inositol hexa-PCA; isopropyl hydroxybutyramide dimethicone copolyol; lactamide MEA; lactic acid; lactitol; lactose; lauryl PCA; lysine PCA; lysine PCA; lysine PCA; magnesium PCA; maltitol; manganese PCA; mannitol; MEL; menthyl PCA; methoxy PEG-10; methoxy PEG-100; methoxy PEG-16; methoxy PEG-40; methyl gluceth-10; methyl gluceth-20; methyl glucose dioleate; methylsilanol PCA; octyl PCA; PCA; PEG-10;

PEG-10 propylene glycol; PEG-100; PEG-12; PEG-135; PEG-14; PEG-150; PEG-16; PEG-18; PEG-180; PEG-2 lactamide; PEG-20; PEG-20 stearate; PEG-200; PEG-240; PEG-25M; PEG-3 stearate; PEG-32; PEG-4; PEG-40; PEG-45M; PEG-6; PEG-60; PEG-75; PEG-8; PEG-8 stearate; PEG-9; PEG-90; placental protein; polydextrose; polyglucuronic acid; polyglycerin-3; polyglyceryl sorbitol; polysilicone-1; polysilicone-2; potassium dimethicone copolyol panthenyl phosphate; potassium dimethicone copolyol phosphate; potassium PCA; PPG-20 methyl glucose ether; PPG-20 methyl glucose ether distearate; PPG-38-buteth-37; propylene glycol; pyridoxine dilaurate; saccharide isomerate; serica; serum albumin; silk amino acids; sodium carboxymethyl chitin; sodium lactate; sodium mannuronate methylsilanol; sodium PCA; sodium PCA; sodium PCA methylsilanol; sodium PG-propyl thiosulfate dimethicone; sodium polyglutamate; soluble collagen; sorbitol; soy sterol; sucrose; sulfated castor oil; tea-lactate; tea-PCA; trehalose; tricontanyl PVP; trifluoromethyl C1-4 alkyl dimethicone; trilactin; urea; xylitol; zea mays; zinc PCA.

The agent can also be a depilatory agent. A depilatory agent is an agent which removes body hair. Examples of depilatory agents include: alkali sulphides; alkaline earth sulphides; ammonium thioglycolate; ammonium thiolactate; barium sulfide; calcium sulfide; calcium thioglycolate; ethanolamine thioglycolate; glyceryl thioglycolate; isooctyl thioglycolate; lithium sulfide; magnesium sulfide; magnesium thioglycolate; mercaptopropionic acid; potassium sulfide; potassium thioglycolate; sodium sulfide; sodium thioglycolate; strontium sulfide; strontium thioglycolate; thioglycerin; thioglycollic acid and its salts; thiolactic acid; and zinc sulfide.

A preferred cosmetic agent is any of the known bulking agents which can be added to the hair or nails to provide 'body' and strength. Bulking agents are well known to those of ordinary skill in the art. Examples of bulking agents generally include cationic surfactant/polymers, fatty alcohols (non-ionic surfactant), waxes or esters, non-ionic polymers (e.g. polyglycols) for thickening, and insoluble silicone. The preferred bulking agent is the cationic surfactant, which places a dispersive charge on the hair. Examples of cationic surfactants include: quaternary ammonium hydroxides, e.g., tetramethylammonium hydroxide, alkyltrimethylammonium hydroxides wherein the alkyl group has from about 8 to 22 carbon atoms, for example octyltrimethylammonium hydroxide, dodecyltrimethy-ammonium hydroxide, hexadecyltrimethylammonium hydroxide, cetyltrimethylammonium hydroxide, octyldimethylbenzylammonium hydroxide, decyldimethyl-benzylammonium hydroxide, stearyldimethylbenzylammonium hydroxide, didodecyldimethylammonium hydroxide, dioctadecyldimethylammonium hydroxide, tallow trimethylammonium hydroxide, cocotrimethylammonium hydroxide, and the corresponding salts thereof, e.g., chlorides; cetylpyridinium hydroxide or salts thereof, e.g., chloride; Quaternium -5, Quaternium -31, Quaternium -18 and mixtures thereof. Additional bulking agents can be solutions of proteins, peptides, and polynucleotides or combinations thereof. Particular bulking agents include collagen, keratins, plant structural proteins, silk, fibrin, mucopolysaccharide and elastin. Other examples of bulking agents include: polylysine; biotin, panthenol, glycoprotein, and mucopolysaccharide; amodimethicone; acrylates; dimethicone copolymer; di-isobutyl adipate; isododecane; polypropylene glycol, glycerol, disaccharides, urea, dithiothreitol, edta, methyl paraben, propylparaben; polyvinylpyrrolidone and copolymers or derivatives thereof; for example, copolymers with the ethyl or butyl ester of PVA/MA (partially neutralized), copolymers with vinyl acetate/crotonic acid, copolymers of PVP/VA in all proportions,

Polyquaternium-11, and copolymers with ethyl methacrylate/oleyl methacrylate/diethylaminoethyl methacrylate quaternized with dimethyl sulfate, as well as carboxyvinyl polymers, such as hydroxyethyl cellulose, hydroxypropyl methylcellulose, and guar gum, zanthan gum, tragacanth gum, and other natural viscosity boosters; ceramide; copolymers of vinyl acetate and crotonic acid, terpolymers of vinyl acetate, crotonic acid and a vinyl ester of an alpha-branched saturated aliphatic monocarboxylic acid such as vinyl neodecanoate, and copolymers of methyl vinyl ether and maleic anhydride (molar ratio about 1:1) wherein such copolymers are 50% esterified with a saturated aliphatic alcohol containing from 1 to 4 carbon atoms such as ethanol or butanol; and acrylic copolymers and terpolymers containing acrylic acid or methacrylic acid as the anionic radical containing moiety such as terpolymers of methacrylic acid, butylacrylate and ethyl methacrylate which is presently the preferred acrylic polymer.

Bulking agents can be used as hair conditioning or hair fixative agents. Hair conditioning agents are agents which improve the appearance, texture and sheen of hair as well as increasing hair body or suppleness. Usually these compounds facilitate hair styling. Examples of hair conditioning agents include: Acetamide MEA; Acetamidoethoxybutyl Trimonium Chloride; Acetylated Lanolin; Acetylated Lanolin Alcohol; Acetylmethionyl Methylsilanol Elastinate; Acrylates/Carbamate Copolymer; Alanine; Albumen; Alfalfa (Medicago Sativa) Oil Unsaponifiables; Almondamidopropalkonium Chloride; Almondamidopropyl Betaine; Aluminum Capryloyl Hydrolyzed Collagen; Aluminum Undecylenoyl Collagen Amino Acids; Amino Bispropyl Dimethicone; Aminopropyl Dimethicone; Aminopropyl Laurylglutamine; Ammonium Caseinate; Ammonium Hydrolyzed Collagen; Ammonium Lauroyl Sarcosinate; Amodimethicone; Amodimethicone/Dimethicone Copolyol; Amodimethicone Hydroxystearate; AMP-Isostearoyl Gelatin/Keratin Amino Acids/Lysine Hydroxypropyltrimonium Chloride; AMP-Isostearoyl Hydrolyzed Collagen; AMP-Isostearoyl Hydrolyzed Soy Protein; AMP-Isostearoyl Hydrolyzed Wheat Protein; AMPD-Isostearcyl Hydrolyzed Collagen; AMPD-Rosin Hydrolyzed Collagen; Apricotamidopropyl Betaine; Apricotamidopropyl Ethyldimonium Ethosulfate; Argemone Mexicana Oil; Arginine; Arginine Aspartate; Asparagine; Aspartic Acid; Atelocollagen; Avocadamidopropyl Betaine; Avocado (Persea Gratissima) Oil Unsaponifiables; Babassuamide DEA; Babassuamidopropalkonium Chloride; Babassuamidopropylamine Oxide; Babassuamidopropyl Betaine; Beer; Behenamide DEA; Behenamide MEA; Behenamidopropyl Betaine; Behenamidopropyl Dimethylamine Behenate; Behenamidopropyl Dimethylamine Lactate; Behenamidopropyl Ethyldimonium Ethosulfate; Behenamidopropyl PG-Dimonium Chloride; Behenoyl PG-Trimonium Chloride; Behentrimonium Chloride; Behentrimonium Methosulfate; Behenyl Betaine; Behenyl Hydroxyethyl Imidazoline; Benzyltrimonium Hydrolyzed Collagen; Biotin; Bisphenylhexamethicone; Butoxy Chitosan; Buttermilk Powder; Butyloctyl Salicylate; Calcium Caseinate; Calcium Pantothenate; Canolamidopropyl Betaine; Canolamidopropyl Ethyldimonium Ethosulfate; Caproyl Sphingosine; Capryl/Capramidopropyl Betaine; Capryl Hydroxyethyl Imidazoline; Capryloyl Collagen Amino Acids; Capryloyl Glycine; Capryloyl Hydrolyzed Collagen; Capryloyl Hydrolyzed Keratin; Capryloyl Keratin Amino Acids; Capryloyl Pea Amino Acids; Capryloyl Quinoa Amino Acids; Capryloyl Silk Amino Acids; Caprylyl Glycol; Caprylyl Hydroxyethyl Imidazoline; Caprylyl Pyrrolidone; Carboxybutyl Chitosan; Carboxymethyl Chitin; Carboxymethyl Chitosan Succinamide; Carboxymethyl Isostearamidopropyl Morpholine; Carnitine; Carpronium Chloride; Casein; Catalase;

Cauliflower (Brassica Oleracea Botrytis) Oil Unsaponifiables; Ceramide 1; Ceramide 2; Ceramide 3; Ceramide 4; Ceramide 5; Ceramide 1 A; Ceramide 6 II; Ceteartrimonium Chloride; Cetearyl Dimethicone/Vinyl Dimethicone Crosspolymer; Cetearyl Isononanoate; Cetearyl Octanoate; Cetearyl Palmitate; Cetyl Betaine; Cetyl Glycol; Cetyl Pyrrolidonylmethyl Dimonium Chloride; Cetyl Triethylammonium Dimethicone Copolyol Phthalate; Cholecalciferol Polypeptide; Cocamidoethyl Betaine; Cocamidopropylamine Oxide; Cocamidopropyl Amine Oxide; Cocamidopropyl Betaine; Cocamidopropyl Dimethylamine Dihydroxymethylpropionate; Cocamidopropyl Dimethylamine Hydrolyzed Collagen; Cocamidopropyl Dimethylamine Lactate; Cocamidopropyl Dimethylamine Propionate; Cocamidopropyl Dimethylamino-hydroxypropyl Hydrolyzed Collagen; Cocamidopropyl Dimethylammonium C8-16 Isoalkylsuccinyl Lactoglobulin Sulfonate; Cocamidopropyldimonium Hydroxypropyl Hydrolyzed Collagen; Cocamidopropyl Ethyldimonium Ethosulfate; Cocamidopropyl Hydroxysultaine; Cocamidopropyl Morpholine; Cocamidopropyl Morpholine Lactate; Cocamidopropyl PG-Dimonium Chloride; Cocamidopropyl PG-Dimonium Chloride Phosphate; Cocamidopropyltrimonium Chloride; Cocamine Oxide; Cocaminobutyric Acid; Cocaminopropionic Acid; Cocoalkonium Chloride; Cocoamphodipropionic Acid; Cocobetainamido Amphopropionate; Coco-Betaine; Cocodimonium Hydroxypropyl Hydrolyzed Casein; Cocodimonium Hydroxypropyl Hydrolyzed Collagen; Cocodimonium Hydroxypropyl Hydrolyzed Hair Keratin; Cocodimonium Hydroxypropyl Hydrolyzed Keratin; Cocodimonium Hydroxypropyl Hydrolyzed Rice Protein; Cocodimonium Hydroxypropyl Hydrolyzed Silk; Cocodimonium Hydroxypropyl Hydrolyzed Soy Protein; Cocodimonium Hydroxypropyl Hydrolyzed Wheat Protein; Cocodimonium Hydroxypropyl Silk Amino Acids; Coco-Ethyldimonium Ethosulfate; Coco-Hydroxysultaine; Coco-Morpholine Oxide; Coconut (Cocos Nucifera) Oil; Coco/Oleamidopropyl Betaine; Coco-Sultaine; Cocotrimonium Chloride; Cocotrimonium Methosulfate; Cocoyl Benzyl Hydroxyethyl Imidazolinium Chloride; Cocoyl Glutamic Acid; Cocoyl Hydrolyzed Collage; Cocoyl Hydrolyzed Keratin; Cocoyl Hydrolyzed Soy Protein; Cocoyl Hydroxyethyl Imidazoline; Cocoyl Hydroxyethylimidazolinium PG-Chloride phosphate; cocoyl sarcosinamide DEA; Cocyl sarcosine; Collagen; Collagen Amino Acids; Corn (Zea Mays) Gluten Protein; Corn (Zea Mays) Oil; Corn (Zea Mays) Oil Unsaponifiables; Crystallins; Cylcomethicone; Cysteine; Cysteine HCl; Cystine; DATEM; DEA-Cocoamphodipropionate; DEA-Cyclocarboxypropyloleate; DEA-Hydrolyzed Lecithin; DEA-Lauraminopropionate; Decyl Betaine; Decyl Mercaptomethylimidazole; Desamido Collagen; Dextran Hydroxy-propyltrimonium Chloride; Diaminopyrimidine Oxide; Dibehenamidopropyldimethylamine Dilinoleate; DibehenylDjarachidyl Dimonium Chloride; Dibehenyldimonium Chloride; Dibehenyldimonium Methosulfate; Dibutyl Lauroyl Glutamide; Di-C12-15 Alkyl Dimonium Chloride; Di-C12-18 Alkyl Dimonium Chloride; Di-C14-18 Alkyl Dimonium Chloride; Dicapryl/Dicaprylyl Dimonium Chloride; Dicapryloyl Cystine; Dicetyldiminium Chloride; Dicocodimethylamine Dilinoleate; Dicocodimonium Chloride; Dicocoylethyl Hydroxyethylmonium Methosolufate; Didecyldimonium Chloride; Diethylaminoethyl Cocoate; Diethylaminoethyl PEG-5 Cocoate; Diethylaminoethyl PEG-5 Laurate; Diethylaminoethyl Stearate; Diethylene Glycol Dibenzoate; Diethylene Glycol Diisononanoate; Diethylene Glycol Dioctanoate; Diethylene Glycol Dioctanoate/ Diisononanoate; Diethylene Tricaseinamide; Dihyrogenated Palmoylethyl Hydroxy-ethylmonium Methosulfate; Dihydrogenated Palmoyl Hydroxyethylmonium Methosulfate; Dihydrogenated Tallowamidoethyl Hydroxyethylmonium

Chloride; Dihydrogenated Tallowamidoethyl Hydroxyethylmonium Methosulfate; Dihydrogenated Tallow Benzylmonium Chloride; Dihyrodgenated Tallowethyl Hydroxyethylmonium Methosulate; Dihydrogenated Tallow Hydroxyethylmonium Methosulfate; Dihydrogenated Tallowoylethyl Hydroxyethylmonium Methosulfate; Dihydroxyethylamino Hydroxypropyl Oleate; Dihydroxyethyl C12-15 Alkoxypropylamine Oxide; Dihidroxyethyl Cocamine Oxide; Dihyroxyethyl Oleyl Glycinate; Dihydroxyethyl Soy Glycinate; Dihydroxyethyl Stearamine Oxide; Dihydroxyethyl Stearyl Glycinate; Dihydroxyethyl Tallowamine/IPDI Copolymer; Dihydroxyethyl Tallowamine Oleate; dihydroxyethyl Tallowamine Oxide; dihydroxyethyl Tallow Glycinate; Dihydroxypropyl PEG-5 Linoleammonium Chloride Phosphate; Diisostearamidopropyl Epoxypropylmonium Chloride; Dilaureth-4 Dimonium Chloride; Dilauryl Acetyl Dimonium Chloride; Dilauryldimonium Chloride; Dilinoleamidopropyl Dimethylamine Dimethicone Copolyol Phosphate; Dimenthicone Bisamino Hydroxypropyl Copolyol; Dimenthicone Copolyol; Dimethicone Copolyol Acetate; Dimethicone Copolyol Adipate; Dimethicone Copolyol Almondate; Dimethicone Copolyol Avocadoate; Dimethicone Copolyol Beeswax; Dimethicone Copolyol Bishydroxyethylamine; Dimethiocone Copolyol Borageate; Dimethicone Copolyol Butyl Ether; Dimethicone Copolyol Cocoa Butterate; Dimethicone Copolyol Dhupa Butterate; Dimethicone Copolyol Ethyl Ether; Dimethicone Copolyol Kokum Butterate; Dimethicone Copolyol Lactate; Dimethicone Copolyol Mango Butterate; Dimethicone Copolyol Methyl Ether; Dimethicone Copolyol Mohwa Butterate; Dimethicone Copolyol Olivate; Dimethicone Copolyol Phthalate; Dimethicone Copolyol Sal Butterate; Dimethicone Copolyol Shea Butterate; Dimethicone Copolyol Undecylenate; Dimethicone Hydroxyptropyl Trimonioum Chloride; Dimethicone/Mercaptopropyl Methicone Copolymer; Dimethicone Propyl PG-Betaine; Dimethicone/Sodium PG-Propyidimethicone Thiosulfate Copolymer; Dimethiconol Arginine; Dimethiconol Cysteine; Dimethiconol Lactate; Dimethiconol Panthenol; Dimethiconol/Silsesquioxane Copolymer; Dimethaxysilyl Ethylenediaminopropyl Dimethicone; Dimethylaminopropylamido PCA Dimethicone; Dimethyl Aspartic Acid; Dimethyl Glutamic Acid; Dimethyl Lauramine Dimer Dilinoleate; Dimethyl Lauramine Isostearate; Dimethyl Lauramine Oleate; DimethylPABAmidopropyl Laurdimonium Tosylate; Dioctyldodeceth-2 Lauroyl Glutamate; Dioctyldodecyl Dodecanedioate; Dioctyldodecyl Lauroyl Glutamate; Dioleoyl EDTHP-Monium Methosulfate; Dioleoylethyl Hydroxyethylmonium Methosulfate; Dioleoylisopropyl Dimonium Methosulfate; Dipalmitoyl Cystine; Dipalmitoylethyl Dimonium Chloride; Dipalmitoylethyl Hydroxyethylmonium Methosulfate; Dipalmoylethyl Hydroxyethylmonium Methosulfate; Disodium Caproamphodiacetate; Disodium Caproamphodipropionate; Disodium Capryloamphodiacetate; Disodium Capryloamphodipropionate; Disodium Cocaminopropyl Iminodiacetate; Disodium Cocoamphocarboxyethylhydroxypropyisulfonate; Disodium Cocoamphodiacetate; Disodium Cocoamphodipropionate; Disodium Cystinyl Disuccinate; Disodium Dicarboxyethyl Cocopropylenediamine; Disodium Hydrogenated Tallow Glutamate; Disodium Isostearoamphodiacetate; Disodium Isostearoamphodipropionate; Disodium Laureth-5 Carboxyamphodiacetate; Disodium Lauriminodipropionate; Disodium Lauroamphodiacetate; Disodium Lauroamphodipropionate; Disodium Oleoamphodipropionate; Disodium PPG-2-Isodeceth-7 Carboxyamphodiacetate; Disodium Steariminodipropionate; Disodium Stearoamphodiacetate; Disodium Stearoyl Glutamate; Disodium Tallowamphodiacetate; Disodium Tallowiminodipropionate; Disodium Wheatgermamphodiacetate;

Disoyamidoethyl Hydroxyethyl Ammonium Lactate; Disoydimonium Chloride; Disoyoylethyl Hydroxyethylmonium Methosulfate; Distearet-6 Dimonium Chloride; Distearet-2 Lauroyl Glutamate; Distearet-5 Lauroyl Glutamate; Distearoylethyl Dimonium Chloride; Distearoylethyl Hydroxyethyimonium Methosulfate; Distearoylpropyl Trimonium Chloride; Distearyldimethylamine Dilinoleate; Distearyldimonium Chloride; Distearyl Epoxypropylmonium Chloride; Ditallowamidoethyl Hydroxypropylamine; Ditallowamidoethyl Hydroxypropylmonium Methosulfate; Ditallow Dimonium Cellulose Sulfate; Ditallowdimonium Chloride; Ditallowethyl Hydroxyethylmonium Methosulfate; Ditallowoylethyl Hydroxyethylmonium Methosulfate; Ditridecyldimonium Chloride; Dodecylbenzyltrimonium Chloride; Dodecylhexadecyltrimonium Chloride; Dodecylxylylditrimonium Chloride; Egg; Egg Oil; Egg Powder; Elastin; Elastin Amino Acids; Erucalkonium Chloride; Erucamidopropyl Hydroxysultaine; Ethyl Almondate; Ethyl Apricot Kernelate; Ethyl Biotinate; Ethyl Ester of Hydrolyzed Animal Protein; Ethyl Ester of Hydrolyzed Keratin; Ethyl Ester of Hydrolyzed Silk; Ethyl Glutamate; Ethyl Hydroxymethyl Oleyl Oxazoline; Ethyl Minkate; Ethyl Morrhuate; Ethyl Myristate; Ethyl Oleate; Ethyl Olivate; Ethyl Palmitate; Ethyl Pelargonate; Ethyl Persate; Ethyl Serinate; Ethyl Stearate; Ethyl Wheat Germate; Fibronectin; Gelatin; Gelatin/Keratin Amino Acids/Lysine Hydroxypropyltrimonium Chloride; Gelatin/Lysine/Polyacrylamide Hydroxypropyltrimonium Chloride; Ginseng Hydroxypropyltrimonium Chloride; Glucaric Acid; Glucose Oxidase; Glutamic Acid; Glutamine; Glutamyl Histamine; Glyceryl Collagenate; Glyceryl Lanolate; Glycine; Glycoproteins; Glycyl Glycine; Guar Hydroxpropyltrimonium Chloride; Hair Keratin Amino Acids; Hexyldecyl Ester of Hydrolyzed Collagen; Hexyldodecyl Salicylate; Hinokitiol; Histidine; Histidine HCI; Human Placental Enzymes; Human Placental Lipids.

Antistatic agents can sometimes also be used as hair conditioning agents. Antistatic agents are agents reduce static electricity by neutralizing electrical charge on a surface. Antistatic agents include: acetamide MEA; acetamidoethoxybutyl trimonium chloride; acetamidopropyl trimonium chloride; acetum; acetylated lanolin; acetylated lanolin alcohol; acetylated lanolin ricinoleate; acetylmethionyl methylsilanol elastinate; acrylamide/sodium acrylate copolymer; acrylamides copolymer; acrylates/ammonium methacrylate copolymer acrylates/pvp copolymer; acrylates copolymer; adipic acid/dimethylaminohydroxypropyl diethylenetriamine copolymer; adipic acid/epoxypropyl diethylenetriamine copolymer; alanine; allantoin acetyl methionine; almondamidopropalkonium chloride; almonda-midopropyl dimethylamine; aluminum capryloyl hydrolyzed collagen; aluminum undecylenoyl collagen amino acids; aminoethylacrylate phosphate/acrylates copolymer aminopropyl laurylglutamine; ammonium acrylates copolymer; ammonium caseinate; ammonium hydrolyzed collagen; ammonium lauroyl sarcosinate; ammonium VA/acrylates copolymer; amodimethicone; amodimethicone/dimethicone copolyol; amp-isostearoyl hydrolyzed collagen; apricotamidopropyl ethyldimonium ethosulfate; arginine; asparagine; aspartic acid; avocadamidopropalkonium chloride; avocadamidopropyl dimethylamine; babassuamidopropalkonium chloride; babassuamidopropyl dimethylamine; behenalkonium chloride; behenamidopropyl dimethylamine; behenamidopropyl dimethylamine behenate; behenamidopropyl dimethylamine lactate; behenamidopropyl ethyldimonium ethosulfate; behenamidopropyl PG-dimonium chloride; behenoyl PG-trimonium chloride; behentrimonium methosulfate; behenyl betaine; behenyl hydroxyethyl imidazoline; benzyl nicotinate; benzyl triethyl ammonium chloride; benzyltrimonium

hydrolyzed collagen; betaine; bishydroxyethyl dihydroxypropyl stearaminium chloride; butyl ester of ethylene/MA copolymer butyl ester of PVM/MA copolymer; C12-15 alkyl salicylate; C12-16 alcohols; C14-20 isoalkylamidopropylethyldimonium ethosulfate; C18-22 isoalkylamidopropylethyl-dimonium ethosulfate; calcium pantothenate; calcium pantothenate; canolamidopropyl ethyldimonium ethosulfate; capramide DEA; capryl hydroxyethyl imidazoline; capryloyl collagen amino acids; capryloyl hydrolyzed collagen; capryloyl hydrolyzed keratin; capryloyl keratin amino acids; caprylyl hydroxyethyl imidazoline; carpronium chloride; casein; ceresin; cetethyl morpholinium ethosulfate; cetethyldimonium bromide; cetrimonium methosulfate; cetrimonium saccharinate; cetrimonium tosylate; cetyl betaine; cetyl pyrrolidonylmethyl dimonium chloride; cetylpyridinium chloride; cholecalciferol polypeptide; cocamidopropyl dimethylamine; cocamidopropyl dimethylamine hydrolyzed collagen; cocamidopropyl dimethylamine propionate; cocamidopropyl dimethylaminohydroxypropyl hydrolyzed collagen; cocamidopropyl dimethylammonium C8-16 isoalkylsuccinyl lactoglobulin sulfonate; cocamidopropyl ethyldimonium ethosulfate; cocamidopropyl morpholine; cocamidopropyl morpholine lactate; cocamidopropyl PG-dimonium chloride; cocamidopropyl PG-dimonium chloride phosphate; cocamidopropyldimonium hydroxypropyl hydrolyzed collagen; cocamidopropyltrimonium chloride; cocamine oxide; coco/oleamidopropyl betaine
coco-ethyldimonium ethosulfate; coco-hydroxysultaine; coco-morpholine oxide; cocoalkonium chloride; cocodimonium hydroxypropyl hydrolyzed casein; cocodimonium hydroxypropyl hydrolyzed collagen; cocodimonium hydroxypropyl hydrolyzed hair keratin; cocodimonium hydroxypropyl hydrolyzed keratin; cocodimonium hydroxypropyl hydrolyzed rice protein; cocodimonium hydroxypropyl hydrolyzed silk; cocodimonium hydroxypropyl hydrolyzed soy protein; cocodimonium hydroxypropyl hydrolyzed wheat protein; cocodimonium hydroxypropyl silk amino acids; cocotrimonium chloride; cocoyl benzyl hydroxyethyl imidazolinium chloride; cocoyl hydrolyzed collagen; cocoyl hydrolyzed keratin; cocoyl hydrolyzed soy protein; cocoyl polyglyceryl-4 hydroxypropyl dihydroxyethylamine; corn starch/acrylamide/sodium acrylate copolymer; cyclomethicone; cysteine; cystine; DEA-lauraminopropionate; DEA-linoleate; decyl betaine; decylamine oxide; dibehenyl/diarachidyl dimonium chloride; dibehenyl methylamine; dibehenyldimonium chloride; dibehenyldimonium methosulfate; dicapryl/dicaprylyl dimonium chloride dicapryloyl cystine; dicetyldimonium chloride; dicocodimonium chloride; dicocoylethyl hydroxyethylmonium methosulfate; didecyldimonium chloride; diethyl aspartate; diethyl glutamate; diethylaminoethyl PEG-5 laurate; diethylene tricaseinamide; dihydrogenated tallow benzylmonium chloride; dihydrogenated tallow benzylmonium hectorite; dihydrogenated tallow hydroxyethylmonium methosulfate; dihydrogenated tallowamidoethyl hydroxyethylmonium chloride; dihydrogenated tallowamidoethyl hydroxyethylmonium methosulfate; dihydrogenated tallowdimonium chloride; dihydrogenated tallowethyl hydroxyethylmonium methosulfate; dihydrogenated tallowoylethyl hydroxyethylmonium methosulfate; dihydroxyethyl C12-15 alkoxypropylamine oxide; dihydroxyethyl cocamine oxide; dihydroxyethyl soya glycinate; dihydroxyethyl stearamine oxide; dihydroxyethyl stearyl glycinate; dihydroxyethyl tallowamine oxide; dilaureth-4 dimonium chloride; dilauryl acetyl dimonium chloride; dilauryldimonium chloride; dilinoleamidopropyl dimethylamine; dimethicone copolyol; dimethicone propyl PG-betaine; dimethyl aspartic acid; dimethyl behenamine; dimethyl cystinate; dimethyl glutamic acid; dimethyl glutarate; dimethyl lauramine; dimethyl lauramine oleate; dimethyl myristamine; dimethyl palmitamine;

dimethyl soyamine; dimethyl stearamine; dioctylamine; dioctyldodecyl dodecanedioate; dioleoyl edthp-monium methosulfate; dioleyl edthp-monium methosulfate; dipalmitoyl cystine; dipalmitoyl hydroxyproline; dipalmitoylethyl hydroxyethylmonium methosulfate; dipalmoylethyl hydroxyethylmonium methosulfate; disodium caproamphodiacetate; disodium capryloamphodiacetate; disodium hydrogenated cottonseed glyceride sulfosuccinate; disodium lauriminodipropionate; disodium lauroamphodiacetate; disodium lauroamphodipropionate; disodium oleamido MIPA-sulfosuccinate; disodium steariminodipropionate; disodium stearoamphodiacetate; disoyadimonium chloride; distearoylethyl hydroxyethylmonium methosulfate; distearyldimonium chloride; ditallowamidoethyl hydroxypropylmonium methosulfate; ditallowdimonium chloride; ditallowethyl hydroxyethylmonium methosulfate; ditallowoylethyl hydroxyethylmonium methosulfate; ditridecyldimonium chloride; docosahexaenoic acid; dodecylbenzyltrimonium chloride; dodecylxylylditrimonium chloride; erucalkonium chloride; erucamidopropyl hydroxysultaine; ethyl aspartate; ethyl ester of hydrolyzed animal protein; ethyl ester of hydrolyzed keratin; ethyl ester of hydrolyzed silk; ethyl ester of PVM/MA copolymer; ethyl glutamate; ethyl hydroxymethyl oleyl oxazoline; ethyl PEG-15 cocamine sulfate; ethyl serinate; gelatin/keratin amino acids/lysine hydroxypropyl trimonium chloride; gelatin/lysine/polyacrylamide hydroxypropyltrimonium chloride; ginseng hydroxypropyltrimonium chloride; glucosamine HCl; glutamic acid; glutamic acid; glutamine; glyceryl distearate; glyceryl lanolate; glycine; glycol oleate; glycol ricinoleate; guar hydroxypropyltrimonium chloride; hair keratin amino acids; hexadimethrine chloride; hexyl nicotinate; hinokitiol; histidine; hyaluronic acid; hydrogenated lanolin; hydrogenated tallowalkonium chloride; hydrogenated tallowamine oxide; hydrogenated tallowtrimonium chloride; hydrolyzed albumen; hydrolyzed casein; hydrolyzed collagen; hydrolyzed corn protein; hydrolyzed elastin; hydrolyzed hair keratin; hydrolyzed human placental protein; hydrolyzed keratin; hydrolyzed lupine protein; hydrolyzed milk protein; hydrolyzed oat protein; hydrolyzed oats; hydrolyzed pea protein; hydrolyzed placental protein; hydrolyzed potato protein; hydrolyzed rice bran protein; hydrolyzed rice protein; hydrolyzed serum protein; hydrolyzed silk; hydrolyzed soy protein; hydrolyzed spinal protein; hydrolyzed sweet almond protein; hydrolyzed vegetable protein; hydrolyzed wheat protein; hydrolyzed yeast protein; hydrolyzed zein; hydroxycetyl hydroxyethyl dimonium chloride; hydroxyethyl cetyldimonium chloride; hydroxyethyl cetyldimonium phosphate; hydroxyethyl stearamide-mipa; hydroxylated lanolin; hydroxyproline; hydroxypropyl biscetearyldimonium chloride; hydroxypropyl bisisostearamidopropyldimonium chloride; hydroxypropyl bisoleyldimonium chloride; hydroxypropyl bisstearyldimonium chloride; hydroxypropyl guar; hydroxypropyl guar hydroxypropyltrimonium chloride; hydroxypropyltrimonium amylopectin/glycerin crosspolymer; hydroxypropyltrimonium gelatin; hydroxypropyltrimonium hydrolyzed casein; hydroxypropyltrimonium hydrolyzed collagen; hydroxypropyltrimonium hydrolyzed keratin; hydroxypropyltrimonium hydrolyzed rice bran protein; hydroxypropyltrimonium hydrolyzed silk; hydroxypropyltrimonium hydrolyzed soy protein; hydroxypropyltrimonium hydrolyzed vegetable protein; hydroxypropyltrimonium hydrolyzed wheat protein; hydroxystearamide MEA; hydroxystearamidopropyl trimonium chloride; hydroxystearamidopropyl trimonium methosulfate; hydroxystearyl methylglucamine; inositol; isobutylated lanolin oil; isodecyl isononanoate; isodecyl salicylate; isoleucine; isononamidopropyl ethyldimonium ethosulfate; isononyl isononanoate; isopropyl ester of PVM/MA copolymer; isopropyl lanolate;

isopropyl palmitate; isostearamide DEA; isostearamide MEA; isostearamide MIPA; isostearamidopropyl betaine; isostearamidopropyl dimethylamine; isostearamidopropyl dimethylamine gluconate; isostearamidopropyl dimethylamine glycolate; isostearamidopropyl dimethylamine lactate; isostearamidopropyl epoxypropyl dimonium chloride; isostearamidopropyl ethyldimonium ethosulfate; isostearamidopropyl ethylmorpholinium ethosulfate; isostearamidopropyl laurylacetodimonium chloride; isostearamidopropyl morpholine; isostearamidopropyl morpholine lactate; isostearamidopropyl PG-dimonium chloride; isostearaminopropalkonium chloride; isostearoyl hydrolyzed collagen; isostearoyl PG-trimonium chloride; isostearyl benzylimidonium chloride; isostearyl diglyceryl succinate; isostearyl ethyldimonium chloride; isostearyl ethylimidonium ethosulfate; isostearyl hydroxyethyl imidazoline; keratin amino acids; lactamide MEA; lactamidopropyl trimonium chloride; lactoglobulin; lactoyl methylsilanol elastinate; lanolin; lanolin alcohol; lanolin cera; lanolin linoleate; lanolin ricinoleate; lanosterol; lapyrium chloride; lauramide DEA; lauramide MEA; lauramide MIPA; lauramidopropyl acetamidodimonium chloride; lauramidopropyl betaine; lauramidopropyl dimethylamine; lauramidopropyl dimethylamine propionate; lauramidopropyl PG-dimonium chloride; lauramidopropylamine oxide; lauramine; lauramine oxide; lauraminopropionic acid; laurdimonium hydroxypropyl hydrolyzed soy protein; laurdimonium hydroxypropyl hydrolyzed wheat protein; lauroyl collagen amino acids; lauroyl hydrolyzed collagen; lauroyl PG-trimonium chloride; lauroyl sarcosine; laurtrimonium bromide; laurtrimonium trichlorophenoxide; lauryl aminopropylglycine; lauryl betaine; lauryl diethylenediaminoglycine; lauryl dimethylamine cyclocarboxypropyloleate; lauryl glycol; lauryl hydroxyethyl imidazoline; lauryl isoquinolinium bromide; lauryl isoquinolinium saccharinate; lauryl methyl gluceth-10 hydroxypropyldimonium chloride; lauryl myristate; lauryl palmitate; lauryl sultaine; lauryldimonium hydroxypropyl hydrolyzed casein; lauryldimonium hydroxypropyl hydrolyzed collagen; lauryldimonium hydroxypropyl hydrolyzed keratin; lauryldimonium hydroxypropyl hydrolyzed silk; lauryldimonium hydroxypropyl hydrolyzed soy protein; lauryldimonium hydroxypropyl hydrolyzed wheat protein; laurylpyridinium chloride; lecithin; lecithinamide DEA; leucine; linoleamide; linoleamide DEA; linoleamide MEA; linoleamide MIPA; linoleamidopropalkonium chloride; linoleamidopropyl dimethylamine; linoleamidopropyl dimethylamine dimer dilinoleate; linoleamidopropyl dimethylamine lactate; linoleamidopropyl ethyldimonium ethosulfate; linoleamidopropyl PG-dimonium chloride phosphate; linoleic acid; linolenic acid; lysine; lysine; lysine PCA; methacryloyl ethyl betaine/acrylates copolymer; methenammonium chloride; methicone; methionine; methyl aspartic acid; methyl glutamic acid; methyl hydroxycetyl glucaminium lactate; methyl hydroxymethyl oleyl oxazoline; methylbenzethonium chloride; methylenebis tallow acetamidodimonium chloride; methylsilanol acetylmethionate; methylsilanol acetyltyrosine; methylsilanol elastinate; methylsilanol hydroxyproline; methylsilanol hydroxyproline aspartate; methylsilanol mannuronate; milk amino acids; minkamidopropalkonium chloride; minkamidopropyl dimethylamine; minkamidopropyl ethyldimonium ethosulfate; monosaccharide lactate condensate; montan acid wax; montan cera; myristamide DEA; myristamide MEA; myristamide MIPA; myristamidopropyl betaine; myristamidopropyl dimethylamine; myristamidopropylamine oxide; myristamine oxide; myristaminopropionic acid; myristoyl hydrolyzed collagen; myristoyl sarcosine; myristyl betaine; myristyl hydroxyethyl imidazoline; niacin; norvaline; norvaline; norvaline; octylacrylamide/acrylates/butylaminoethyl methacrylate copolymer; octyldecyl

trimonium chloride; octyldodecyltrimonium chloride; oleamide DEA; oleamide MEA; oleamide MIPA; oleamidopropyl betaine; oleamidopropyl dimethylamine; oleamidopropyl dimethylamine glycolate; oleamidopropyl dimethylamine hydrolyzed collagen; oleamidopropyl dimethylamine lactate; oleamidopropyl dimethylamine propionate; oleamidopropyl ethyldimonium ethosulfate; oleamidopropyl hydroxysultaine; oleamidopropyl PG-dimonium chloride; oleamidopropylamine oxide; oleamidopropyldimonium hydroxypropyl hydrolyzed collagen; oleamine; oleamine bishydroxypropyltrimonium chloride; oleamine oxide; oleoyl hydrolyzed collagen; oleoyl PG-trimonium chloride; oleoyl sarcosine; oleyl betaine; oleyl hydroxyethyl imidazoline; oleyl lanolate; olivamidopropyl dimethylamine; olivamidopropyl dimethylamine lactate; oryzanol; ouricury wax; palm kernelamidopropyl betaine; palmamidopropyl betaine; palmitamide DEA; palmitamide MEA; palmitamidopropyl betaine; palmitamidopropyl diethylamine; palmitamidopropyl dimethylamine; palmitamidopropyl dimethylamine lactate; palmitamidopropyl dimethylamine propionate; palmitamidopropylamine oxide; palmitamine; palmitamine oxide; palmitoleamidopropyl dimethylamine lactate; palmitoleamidopropyl dimethylamine propionate; palmitoyl collagen amino acids; palmitoyl hydrolyzed collagen; palmitoyl hydrolyzed milk protein; palmitoyl keratin amino acids; palmitoyl PG-trimonium chloride; panthenol; panthenyl ethyl ether; panthenyl ethyl ether acetate; panthenyl hydroxypropyl steardimonium chloride; panthenyl triacetate; pantothenic acid; pantothenic acid polypeptide; paraffinum liquidum; PCA ethyl cocoyl arginate; PEG-10 coco-benzonium chloride; PEG-10 coconut oil esters; PEG-10 stearamine; PEG-10 stearyl benzonium chloride; PEG-105 behenyl propylenediamine; PEG-15 cocomonium chloride; PEG-15 cocopolyamine; PEG-15 oleammonium chloride; PEG-15 stearamine; PEG-15 stearmonium chloride; PEG-15 tallow polyamine; PEG-2 coco-benzonium chloride; PEG-2 cocomonium chloride; PEG-2 milk solids; PEG-2 oleammonium chloride; PEG-2 stearamine; PEG-2 stearmonium chloride; PEG-20 tallow ammonium ethosulfate; PEG-25 diethylmonium chloride; PEG-3 lauramine oxide; PEG-3 tallow propylenedimonium dimethosulfate; PEG-5 cocomonium methosulfate; PEG-5 ditridecylmonium chloride; PEG-5 stearamine; PEG-5 stearyl ammonium chloride; PEG-5 stearyl ammonium lactate; PEG-5 tall oil sterol ether; PEG-5 tallow benzonium chloride; PEG-50 stearamine; PEG-8 palmitoyl methyl diethonium methosulfate; petrolatum; PG-hydroxyethylcellulose cocodimonium chloride; PG-hydroxyethylcellulose lauryldimonium chloride; PG-hydroxyethylcellulose stearyldimonium chloride; phenyl trimethicone; phenylalanine; phenylalanine; phosphatidylcholine; phthalic anhydride/glycerin/glycidyl decanoate copolymer pix ex carbone; polyacrylamide; polybutylene terephthalate; polyethylacrylate; polyethylene; polymethacrylamidopropyltrimonium chloride; polyquaternium-1; polyquaternium-10; polyquaternium-11; polyquaternium-12; polyquaternium-13; polyquaternium-14; polyquaternium-15; polyquaternium-16; polyquaternium-17; polyquaternium-18; polyquaternium-19; polyquaternium-2; polyquaternium-20; polyquaternium-22; polyquaternium-24; polyquaternium-27; polyquaternium-28; polyquaternium-29; polyquaternium-30; polyquaternium-31; polyquaternium-32; polyquaternium-33; polyquaternium-34; polyquaternium-35; polyquaternium-36; polyquaternium-37; polyquaternium-39; polyquaternium-4; polyquaternium-42; polyquaternium-5; polyquaternium-6; polyquaternium-7; polyquaternium-8; polyquaternium-9; polysilicone-7; polyvinyl acetate; polyvinyl butyral; polyvinyl imidazolinium acetate; polyvinyl methyl ether; potassium caseinate; potassium cocoyl hydrolyzed casein; potassium cocoyl hydrolyzed collagen; potassium cocoyl hydrolyzed keratin;

potassium cocoyl hydrolyzed rice bran protein; potassium cocoyl hydrolyzed rice protein; potassium cocoyl hydrolyzed silk; potassium cocoyl hydrolyzed soy protein; potassium cocoyl hydrolyzed wheat protein; potassium lauroyl collagen amino acids; potassium lauroyl hydrolyzed collagen; potassium lauroyl hydrolyzed soy protein; potassium lauroyl wheat amino acids; potassium lauryl hydroxypropyl sulfonate; potassium myristoyl hydrolyzed collagen; potassium oleoyl hydrolyzed collagen; potassium stearoyl hydrolyzed collagen; potassium tallate; potassium undecylenoyl hydrolyzed collagen; PPG-12-buteth-16; PPG-14 butyl ether; PPG-15 butyl ether; PPG-15-buteth-20; PPG-16 butyl ether; PPG-18 butyl ether; PPG-2-buteth-3; PPG-20 methyl glucose ether; PPG-20-buteth-30; PPG-22 butyl ether; PPG-24-buteth-27; PPG-25 diethylmonium chloride; PPG-26-buteth-26; PPG-28-buteth-35; PPG-3 tallow aminopropylamine; PPG-3-buteth-5; PPG-30 butyl ether; PPG-33 butyl ether; PPG-33-buteth-45; PPG-4 butyl ether; PPG-40 butyl ether; PPG-40 diethylmonium chloride; PPG-5 butyl ether; PPG-5-buteth-7; PPG-53 butyl ether; PPG-7-buteth-10; PPG-9 butyl ether; PPG-9 diethylmonium chloride; PPG-9-buteth-12; proline; proline; propyltrimonium hydrolyzed collagen; propyltrimonium hydrolyzed soy protein; propyltrimonium hydrolyzed wheat protein; PVM/MA copolymer; PVP/dimethylaminoethylmethacrylate copolymer; PVP/eicosene copolymer; PVP/hexadecene copolymer; PVP/VA/itaconic acid copolymer; PVP/VA/vinyl propionate copolymer; PVP/va copolymer; pyridoxine; pyridoxine dicaprylate; pyridoxine dilaurate; pyridoxine dioctenoate; pyridoxine dipalmitate; pyridoxine HCl; pyridoxine tripalmitate; quaternium-1; quaternium-14; quaternium-16; quaternium-18; quaternium-18 methosulfate; quaternium-22; quaternium-24; quaternium-26; quaternium-27; quaternium-30; quaternium-33; quaternium-43; quaternium-45; quaternium-51; quaternium-52; quaternium-53; quaternium-56; quaternium-60; quaternium-61; quaternium-62; quaternium-63; quaternium-70; quaternium-71; quaternium-72; quaternium-73; quaternium-75; quaternium-76 hydrolyzed collagen; quaternium-77; quaternium-78; quaternium-79 hydrolyzed collagen; quaternium-79 hydrolyzed keratin; quaternium-79 hydrolyzed milk protein; quaternium-79 hydrolyzed silk; quaternium-79 hydrolyzed soy protein; quaternium-79 hydrolyzed wheat protein; quaternium-8; quaternium-80; quaternium-81; quaternium-82; quaternium-83; quaternium-84; quaternium-85; rapeseedamidopropyl benzyldimonium chloride; rapeseedamidopropyl epoxypropyl dimonium chloride; rapeseedamidopropyl ethyldimonium ethosulfate; resorcinol acetate; ricinoleamide DEA; ricinoleamide MEA; ricinoleamide MIPA; ricinoleamidopropyl betaine; ricinoleamidopropyl dimethylamine; ricinoleamidopropyl dimethylamine lactate; ricinoleamidopropyl ethyldimonium ethosulfate; ricinoleamidopropyltrimonium chloride; ricinoleamidopropyltrimonium methosulfate; safflowerami dopropyl ethyldimonium ethosulfate; serica; sericin; serine; silicone quaternium-1; silicone quaternium-2; silicone quaternium-3; silicone quaternium-4; silicone quaternium-5; silicone quaternium-6; silicone quaternium-7; silicone quaternium-8; silicone quaternium-9; sine adipe lac; sodium/tea-lauroyl collagen amino acids; sodium/tea-lauroyl hydrolyzed collagen; sodium/tea-lauroyl hydrolyzed keratin; sodium/tea-lauroyl keratin amino acids; sodium/tea-undecylenoyl collagen amino acids; sodium/tea-undecylenoyl hydrolyzed collagen; sodium acrylate/vinyl alcohol copolymer; sodium carrageenan; sodium caseinate; sodium chondroitin sulfate; sodium cocoyl collagen amino acids; sodium cocoyl hydrolyzed collagen; sodium cocoyl hydrolyzed keratin; sodium cocoyl hydrolyzed rice protein; sodium cocoyl hydrolyzed soy protein; sodium isethionate; sodium lauraminopropionate; sodium lauriminodipropionate; sodium lauroamphohydroxypropylsulfonate; sodium lauroamphopropionate; sodium lauroyl collagen amino acids;

sodium lauroyl glutamate; sodium lauroyl hydrolyzed collagen; sodium lauroyl hydrolyzed silk; sodium lauroyl isethionate; sodium lauroyl sarcosinate; sodium lauroyl taurate; sodium lauroyl wheat amino acids; sodium methyl oleoyl taurate; sodium myristoamphoacetate; sodium myristoyl hydrolyzed collagen; sodium myristoyl isethionate; sodium myristoyl sarcosinate; sodium oleoamphoacetate; sodium oleoamphopropionate; sodium oleoyl hydrolyzed collagen; sodium oleoyl isethionate; sodium PCA; sodium PCA; sodium soya hydrolyzed collagen; sodium stearoamphoacetate; sodium stearoyl hydrolyzed collagen; sodium tallamphopropionate; sodium urocanate; soluble collagen; soy dihydroxypropyldimonium polyglucose; soyaethyl morpholinium ethosulfate; soyamidopropalkonium chloride; soyamidopropyl ethyldimonium ethosulfate; soyamine; soydimonium hydroxypropyl hydrolyzed wheat protein; soyethyldimonium ethosulfate; soytrimonium chloride; squalene; starch diethylaminoethyl ether; steapyrium chloride; stearamide DEA; stearamide MEA; stearamide MEA-stearate; stearamide MIPA; stearamidoethyl diethanolamine; stearamidoethyl diethylamine; stearamidoethyl diethylamine phosphate; stearamidoethyl ethanolamine; stearamidoethyl ethanolamine phosphate; stearamidopropalkonium chloride; stearamidopropyl betaine; stearamidopropyl cetearyl dimonium tosylate; stearamidopropyl dimethylamine; stearamidopropyl dimethylamine lactate; stearamidopropyl ethyldimonium ethosulfate; stearamidopropyl morpholine; stearamidopropyl morpholine lactate; stearamidopropyl PG-dimonium chloride phosphate; stearamidopropyl pyrrolidonylmethyl dimonium chloride; stearamidopropyl trimonium methosulfate; stearamidopropylamine oxide; stearamine; stearamine oxide; steardimonium hydroxypropyl hydrolyzed casein; steardimonium hydroxypropyl hydrolyzed collagen; steardimonium hydroxypropyl hydrolyzed keratin; steardimonium hydroxypropyl hydrolyzed rice protein; steardimonium hydroxypropyl hydrolyzed silk; steardimonium hydroxypropyl hydrolyzed vegetable protein; steardimonium hydroxypropyl hydrolyzed wheat protein; stearoyl PG-trimonium chloride; stearoyl sarcosine; steartrimonium hydroxyethyl hydrolyzed collagen; steartrimonium methosulfate; stearyl betaine; stearyl hydroxyethyl imidazoline; stearyl hydroxyethylimidonium chloride; stearyl octyldimonium chloride; stearyl octyldimonium methosulfate; stearylvinyl ether/MA copolymer; sucrose cocoate; sulfur; synthetic wax; tall oil benzyl hydroxyethyl imidazolinium chloride; tall oil hydroxyethyl imidazoline; tallamide DEA; tallow trihydroxyethylammonium acetate; tallowalkonium chloride; tallowamide DEA; tallowamide MEA; tallowamidopropylamine oxide; tallowamine oxide; tallowdimonium propyltrimonium dichloride; tallowtrimonium chloride; tea-abietoyl hydrolyzed collagen; tea-cocoyl hydrolyzed collagen; tea-cocoyl hydrolyzed soy protein; tea-lauraminopropionate; tea-lauroyl keratin amino acids; tea-lauroyl sarcosinate; tea-myristaminopropionate; tea-myristoyl hydrolyzed collagen; tea-oleoyl hydrolyzed collagen; tea-oleoyl sarcosinate; tea-palm kernel sarcosinate; tea-undecylenoyl hydrolyzed collagen; tetrabutyl ammonium bromide; thenoyl methionate; threonine; threonine; tricetylmonium chloride; tridecyl salicylate; triethonium hydrolyzed collagen ethosulfate; trilaurylamine; trimethylsilylamodimethicone; trioctanoin; tripaba panthenol; trisodium lauroampho PG-acetate phosphate chloride; tristearyl PG-phosphate dimonium chloride; triundecanoin; tryptophan; tryptophan; tyrosine; undecylenamide DEA; undecylenamide MEA; undecylenamidopropyltrimonium methosulfate; undecylenoyl collagen amino acids; undecylenoyl hydrolyzed collagen; undecylenyl alcohol; urea; VA/crotonates/vinyl neodecanoate copolymer; va/crotonates copolymer; valine; wheat germamidopropalkonium chloride; wheat germamidopropyl epoxypropyldimonium chloride;

wheat germamidopropylamine oxide; wheat germamidopropyldimonium hydroxypropyl hydrolyzed wheat protein; wheatgermamidopropyl dimethylamine hydrolyzed collagen; wheatgermamidopropyl dimethylamine hydrolyzed wheat protein; wheatgermamidopropyl ethyldimonium ethosulfate; zea mays; zinc hydrolyzed collagen.

In particular, cationic and amphoteric fatty acids such as polyquaternium compounds are useful as hair conditioners or fixatives. Examples of cationic amino and quaternary ammonium monomers include, for example, vinyl compounds substituted with dialkyl aminoalkyl acrylate, dialkylamino alkylmethacrylate, monoalkylaminoalkyl acrylate, monoalkylaminoalkyl methacrylate, trialkyl methacryloxyalkyl ammonium salt, trialkyl acryloxyalkyl ammonium salt, diallyl quaternary ammonium salts, and vinyl quaternary ammonium monomers having cyclic cationic nitrogen-containing rings such as pyridinium, imidazolium, and quaternized pyrrolidine, e.g., alkyl vinyl imidazolium, alkyl vinyl pyridinium, and alkyl vinyl pyrrolidine salts. The alkyl portions of these, monomers are preferably lower alkyls such as the C1-C3 alkyls, more preferably C1 and C2 alkyls.

Other compounds useful as bulking agents include: octylacrylamide/acrylates/butylaminoethyl methacrylate copolymer (a polymer of N-tert-octyl acrylamide, methyl methacrylate, hydroxypropyl methacrylate, acrylic acid and t-butyl aminoethyl methacrylate).

Other cationic conditioning compounds include quaternary nitrogen derivatives of cellulose ethers, homopolymers of dimethyldiallyl-ammonium chloride, copolymers of acrylamide and dimethyldiallylammonium chloride, homopolymers or copolymers derived from acrylic acid or methacrylic acid containing cationic nitrogen functional groups attached to the polymer via ester or amide linkages, polycondensation products of N,N'-bis-(2,3-epoxypropyl)-piperazine or of piperazine-bis-acrylamide and piperazine, poly-(dimethylbutenylammonium chloride)-α,θ-bis-(triethanol-ammonium) chloride.

Other compounds which are useful as hair fixatives include shellac, polyvinylpyrrolidone-ethyl methacrylate-methacrylic acid tarpolymer, vinyl acetate-crotonic acid copolymer, vinyl acetate-crotonic acid-vinyl neodeconate tarpolymer, poly(vinylpyrrolidone-ethylmethacrylate) methacrylic acid copolymer, vinyl methyl ether-maleic anhydride copolymer, octylacrylamide-acrylate-butylaminoethyl-methacrylate copolymer, and poly(vinylpyrrolidone-dimethylaminoethyl-methacrylate) copolymer and derivatives; thioglycollic acid and its salts and esters; potassium or sodium hydroxide; lithium hydroxide; calcium hydroxide; quinine and its salts; resorcinol; 1,3-bis(hydroxymethyl)imidazolidine-2-thione; etidronic acid and its salts (1-hydroxy-ethylidene-diphosphonic acid and its salts).

Examples of anti-foaming agents which are useful as bulking agents include: bisphenylhexamethicone; dimethicone; dimethiconol; hexamethyldisiloxane; hexyl alcohol; isopropyl alcohol; petroleum distillates; phenethyl disiloxane; phenyl trimethicone; polysilicone-7; propyl alcohol; silica dimethyl silylate; silica silylate; tetramethyl decynediol; trimethylsiloxysilicate.

The agent also can be a tissue sealant. Tissue sealants are those used in wound healing to mechanically seal wounds. The use of transglutaminase to covalently attach such materials would add mechanical and adhesive strength to this sealant. Such tissue sealants are composed typically of fibrinogen, collagen, hyaluronic

acid, synthetic peptides and the like. They also can be polyglutamines, polylysines, or polymers of both glutamine and lysine, corneocyte proteins and the like.

The agents also can be insect repellants. A widely used insect repellant is N-N-diethyl-3-methylbenzamide. Pheromones are also useful as insect repellants.

The agent also may be cultured cells and cultured body tissues used for wound healing, cartilage replacement, corneal replacements and other like surgical procedures.

The agent can also be a film forming agent. A film forming agent is an agent which produces a continuous film on skin, hair or nails upon application. Film forming agents are useful in wound healing or in some cases as hair fixatives. Examples of film forming agents include: acetyl tributyl citrate; acetyl triethyl citrate; acetyl trioctyl citrate; acrylamide/sodium acrylate copolymer; acrylamides/acrylates/DMAPA/methoxy PEG methacrylate copolymer; acrylamides copolymer; acrylamidopropyltrimonium chloride/acrylates copolymer; acrylates/acetoacetoxyethyl methacrylate copolymer; acrylates/acrylamide copolymer; acrylates/ammonium methacrylate copolymer; acrylates/C10-30 alkyl acrylate crosspolymer; acrylates/diacetoneacrylamide copolymer; acrylates/octylacrylamide copolymer; acrylates/PVP copolymer; acrylates/steareth-50 acrylate copolymer; acrylates/VA copolymer; acrylates/VA crosspolymer; acrylates copolymer; acrylic acid/acrylonitrogens copolymer; adipic acid/diethylene glycol/glycerin crosspolymer; adipic acid/diethylenetriamine copolymer; adipic acid/dimethylaminohydroxypropyl diethylenetriamine copolymer; adipic acid/epoxypropyl diethylenetriamine copolymer; adipic acid/isophthalic acid/neopentyl glycol/trimethylolpropane; copolymer; albumen; allyl stearate/VA copolymer; aminoethylacrylate phosphate/acrylates copolymer; ammonium acrylates/acrylonitrogens copolymer; ammonium acrylates copolymer; ammonium alginate; ammonium VA/acrylates copolymer; amp-acrylates/diacetoneacrylamide copolymer; amp-acrylates copolymer; ampd-acrylates/diacetoneacrylamide copolymer; bayberry wax; behenyl/isostearyl beeswax; benzoic acid/phthalic anhydride/pentaerythritol/neopentyl glycol/palmitic acid copolymer; butadiene/acrylonitrile copolymer; butoxy chitosan; butyl benzoic acid/phthalic anhydride/trimethylolethane copolymer; butyl benzyl phthalate; butyl ester of ethylene/MA copolymer; butyl ester of PVM/MA copolymer; butyl phthalyl butyl glycolate; butylated polyoxymethylene urea; butylated PVP; calcium/sodium PVM/MA copolymer; calcium carrageenan; camphor; candelilla cera; carboxymethyl chitosan succinamide; carboxymethyl hydroxyethylcellulose; carnauba; cellulose acetate; cellulose acetate butyrate; cellulose acetate propionate; cellulose gum; cera alba; ceratonia siliqua; cetyl hydroxyethylcellulose; chitosan succinamide; collodion; colophonium; copaifera officinalis; copal; corn starch/acrylamide/sodium acrylate copolymer; croscarmellose; cyanopsis tetragonalba; desamido collagen; dibutyl adipate; dibutyl lauroyl glutamide; dibutyl phthalate; dibutyl sebacate; dicapryl adipate; dicetyl adipate; diethyl phthalate; diethylene glycolamine/epichlorohydrin/piperazine copolymer; diglycol/chdm/isophthalates/sip copolymer; dilinoleic acid/ethylenediamine copolymer; dimethicone/mercaptopropyl methicone copolymer; dimethicone/sodium PG-propyldimethicone thiosulfate copolymer; dimethyl phthalate; dioctyl adipate; dioctyl phthalate; dioctyl sebacate; dioctyl succinate; dmapa acrylates/acrylic acid/acrylonitrogens copolymer; dmhf; dodecanedioic acid/cetearyl alcohol/glycol copolymer; ethyl cyanoacrylate; ethyl ester of PVM/MA copolymer; ethyl tosylamide; ethylcellulose; ethylene/acrylic acid/VA copolymer; ethylene/acrylic acid copolymer;

ethylene/calcium acrylate copolymer; ethylene/MA copolymer; ethylene/magnesium acrylate copolymer; ethylene/propylene copolymer; ethylene/sodium acrylate copolymer; ethylene/VA copolymer; ethylene/zinc acrylate copolymer; flexible collodion; gellan gum; glyceryl alginate; glyceryl hydrogenated rosinate; glyceryl polyacrylate; glyceryl rosinate; glycosaminoglycans; guar hydroxypropyltrimonium chloride; gutta percha; ydrogenated styrene/butadiene copolymer; hydrogenated styrene/methyl styrene/indene copolymer; ydrolyzed collagen; hydrolyzed elastin; hydrolyzed keratin; hydroxybutyl methylcellulose; hydroxyethyl ethylcellulose; hydroxyethylcellulose; hydroxylated lanolin; hydroxypropyl guar; hydroxypropyl methylcellulose; hydroxypropylcellulose; isobutylene/sodium maleate copolymer; isopropyl ester of PVM/MA copolymer; lanolin cera; lauryl acrylate/VA copolymer; lithium oxidized polyethylene; maltodextrin; melamine/formaldehyde resin; methacryloyl ethyl betaine/acrylates copolymer; methyl hydrogenated rosinate; methyl methacrylate crosspolymer; methyl rosinate; mustela; natto gum; nitrocellulose; nonoxynyl hydroxyethylcellulose; oat beta glucan; octylacrylamide/acrylates/butylaminoethyl methacrylate copolymer; oleoyl hydrolyzed collagen; ouricury wax; oxidized polypropylene; PEG-8/SMDI copolymer; PEG-crosspolymer; pentaerythrityl hydrogenated rosinate; pentaerythrityl rosinate; phthalic anhydride/adipic acid/castor oil/neopentyl glycol/PEG-3/trimethylolpropane copolymer; phthalic anhydride/benzoic acid/trimethylolpropane copolymer; phthalic anhydride/butyl benzoic acid/propylene glycol copolymer; phthalic anhydride/glycerin/glycidyl decanoate copolymer; phthalic anhydride/trimellitic anhydride/glycols copolymer; polyacrylamide; polyacrylamidomethylpropane sulfonic acid; polyacrylic acid; polybutylene terephthalate; polychlorotrifluoroethylene; polydimethylaminoethyl methacrylate; polyethylacrylate; polyethylene; polyethylene terephthalate; polyglucuronic acid; polyglycerylmethacrylate; polyisobutene; polymethacrylamidopropyltrimonium chloride; polymethyl acrylate; polymethyl methacrylate; polyoxyisobutylene/methylene urea copolymer; polypropylene; Polyquaternium-1; Polyquaternium-10; Polyquaternium-11; Polyquaternium-12; Polyquaternium-13; Polyquaternium-14; Polyquaternium-15; Polyquaternium-16; Polyquaternium-17; Polyquaternium-18; Polyquaternium-19; Polyquaternium-2; Polyquaternium-20; Polyquaternium-22; Polyquaternium-24; Polyquaternium-27; Polyquaternium-28; Polyquaternium-29; Polyquaternium-30; Polyquaternium-31; Polyquaternium-32; Polyquaternium-33; Polyquaternium-34; Polyquaternium-35; Polyquaternium-36; Polyquaternium-37; Polyquaternium-39; Polyquaternium-4; Polyquaternium-42; Polyquaternium-5; Polyquaternium-6; Polyquaternium-7; Polyquaternium-8; Polyquaternium-9; Polysilicone-6; polystyrene; polyurethane; polyvinyl acetate; polyvinyl alcohol; polyvinyl butyral; polyvinyl imidazolinium acetate; polyvinyl laurate; polyvinyl methyl ether; potassium acetate; potassium carrageenan; potassium hyaluronate; PPG-26/TDI copolymer; PPG-51/SMDI copolymer; procollagen; propylene glycol diundecanoate; PVM/MA copolymer; PVP; PVP/decene copolymer; PVP/dimethylaminoethylmethacrylate copolymer; PVP/eicosene copolymer; PVP/hexadecene copolymer; PVP/VA/itaconic acid copolymer; PVP/VA/vinyl propionate copolymer; PVP/va copolymer; rosin acrylate; rosin hydrolyzed collagen; rubber latex; shellac; shellac cera; sodium acrylate/vinyl alcohol copolymer; sodium carrageenan; sodium dvb/acrylates copolymer; sodium polyacrylate starch; sodium polymethacrylate; sodium polystyrene sulfonate; sodium PVM/MA/decadiene crosspolymer; sodium styrene/acrylamide copolymer; sodium styrene/acrylates copolymer; sodium tauride acrylates/acrylic acid/acrylonitrogens copolymer; soluble

collagen; starch/acrylates/acrylamide copolymer; starch diethylaminoethyl ether; steareth-10 allyl ether/acrylates copolymer; stearylvinyl ether/MA copolymer; styrax benzoin; styrax benzoin; styrene/acrylates/acrylonitrile copolymer; styrene/acrylates/ ammonium methacrylate copolymer; styrene/allyl benzoate copolymer; styrene/MA copolymer; styrene/pvp copolymer; sucrose acetate isobutyrate; sucrose benzoate; sucrose benzoate/sucrose acetate isobutyrate/butyl benzyl phthalate/methyl methacrylate copolymer; sucrose benzoate/sucrose acetate isobutyrate/butyl benzyl phthalate; copolymer; sucrose benzoate/sucrose acetate isobutyrate copolymer; tea-acrylates/acrylonitrogens copolymer; tosylamide/epoxy resin; tosylamide/formaldehyde resin; triacetin; tributyl citrate; tributylcresylbutane; tricetyl phosphate; tricontanyl PVP; trimethylpentanediol/isophthalic acid/trimellitic anhydride copolymer; tromethamine acrylates/acrylonitrogens copolymer; VA/butyl maleate/isobornyl acrylate copolymer; VA/crotonates/methacryloxybenzophenone-1 copolymer; VA/crotonates/vinyl neodecanoate copolymer; VA/crotonates/vinyl propionate copolymer; VA/crotonates copolymer; VA/dbm copolymer; VA/isobutyl maleate/vinyl neodecanoate copolymer; VA/vinyl butyl benzoate/crotonates copolymer; vinyl acetate; vinyl caprolactam/pvp/dimethylaminoethyl methacrylate copolymer.

The agent can also be an anti-nerve gas agent. An anti-nerve gas agent is an agent which counteracts the effects of a nerve gas agent. Examples of anti-nerve gas agents include: organophosphate hydrolases such as phosphotriesterase; pyridostigmine, physostigmine, eptastigmine, pralidoxime-2-chloride (2-PAM); potassium 2,3-butadion monoximate; potassium permanganate; sodium phenolate or sodium cresolate; chlorinated lime and magnesium oxide; chloramines; bentonite; and a mixture of atropine and PAM.

The agent can also be a vitamin including vitamin A,vitamin B, vitamin C, vitamin D, vitamin E, and their provitamin counterparts.

As mentioned above, the agent may be a pharmaceutical agent. Examples of categories of pharmaceutical agents include: analgesic; amino acid; antagonist; anti-acne agent; anti-allergic; anti-asthmatic; antibacterial; anticholinergic; antifungal; antiglaucoma agent; antihistamine; anti-infective; anti-infective, topical; anti-inflammatory; antikeratinizing agent; antimicrobial; antimycotic; antineoplastic, antineutropenic; antiproliferative; antipruritic; antiseborrheic; carbonic anhydrase inhibitor; cholinergic; cholinergic agonist; diagnostic aids; ectoparasiticide; fluorescent agent; glucocorticoid; hair growth stimulant; histamine H2 receptor antagonists; immunizing agent; immunomodulator; immunoregulator; immunostimulant; immunosuppressant; keratolytic; mucosal protective agent; radioactive agents; wound healing agent.

Analgesic: Acetaminophen; Alfentanil Hydrochloride; Aminobenzoate Potassium; Aminobenzoate Sodium; Anidoxime; Anileridine; Anileridine Hydrochloride; Anilopam Hydrochloride; Anirolac; Antipyrine; Aspirin; Benoxaprofen; Benzydamine Hydrochloride; Bicifadine Hydrochloride; Brifentanil Hydrochloride; Bromadoline Maleate; Bromfenac Sodium; Buprenorphine Hydrochloride; Butacetin; Butixirate; Butorphanol; Butorphanol Tartrate; Carbamazepine; Carbaspirin Calcium; Carbiphene Hydrochloride; Carfentanil Citrate; Ciprefadol Succinate; Ciramadol; Ciramadol Hydrochloride; Clonixeril; Clonixin; Codeine ; Codeine Phosphate; Codeine Sulfate; Conorphone Hydrochloride; Cyclazocine; Dexoxadrol Hydrochloride; Dexpemedolac; Dezocine; Diflunisal; Dihydrocodeine Bitartrate; Dimefadane; Dipyrone; Doxpicomine Hydrochloride; Drinidene;

Enadoline Hydrochloride; Epirizole; Ergotamine Tartrate; Ethoxazene Hydrochloride; Etofenamate; Eugenol; Fenoprofen; Fenoprofen Calcium; Fentanyl Citrate; Floctafenine; Flufenisal; Flunixin; Flunixin Meglumine; Flupirtine Maleate; Fluproquazone; Fluradoline Hydrochloride; Flurbiprofen ; Hydromorphone Hydrochloride; Ibufenac; Indoprofen; Ketazocine; Ketorfanol; Ketorolac Tromethamine; Letimide Hydrochloride; Levomethadyl Acetate; Levomethadyl Acetate Hydrochloride; Levonantradol Hydrochloride; Levorphanol Tartrate; Lofemizole Hydrochloride; Lofentanil Oxalate; Lorcinadol; Lornoxicam; Magnesium Salicylate; Mefenamic Acid; Menabitan Hydrochloride; Meperidine Hydrochloride; Meptazinol Hydrochloride; Methadone Hydrochloride; Methadyl Acetate; Methopholine; Methotrimeprazine; Metkephamid Acetate; Mimbane Hydrochloride; Mirfentanil Hydrochloride; Molinazone; Morphine Sulfate; Moxazocine; Nabitan Hydrochloride; Nalbuphine Hydrochloride; Nalmexone Hydrochloride ; Namoxyrate; Nantradol Hydrochloride; Naproxen ; Naproxen Sodium ; Naproxol; Nefopam Hydrochloride; Nexeridine Hydrochloride; Noracymethadol Hydrochloride; Ocfentanil Hydrochloride; Octazamide; Olvanil; Oxetorone Fumarate; Oxycodone; Oxycodone Hydrochloride; Oxycodone Terephthalate; Oxymorphone Hydrochloride; Pemedolac; Pentamorphone; Pentazocine; Pentazocine Hydrochloride; Pentazocine Lactate; Phenazopyridine Hydrochloride; Phenyramidol Hydrochloride; Picenadol Hydrochloride; Pinadoline; Pirfenidone; Piroxicam Olamine; Pravadoline Maleate; Prodilidine Hydrochloride; Profadol Hydrochloride; Propiram Fumarate; Propoxyphene Hydrochloride; Propoxyphene Napsylate; Proxazole ; Proxazole Citrate ; Proxorphan Tartrate; Pyrroliphene Hydrochloride; Remifentanil Hydrochloride; Salcolex ; Salethamide Maleate; Salicylamide; Salicylate Meglumine; Salsalate ; Sodium Salicylate; Spiradoline Mesylate; Sufentanil; Sufentanil Citrate; Talmetacin ; Talniflumate ; Talosalate ; Tazadolene Succinate; Tebufelone ; Tetrydamine ; Tifurac Sodium; Tilidine Hydrochloride; Tiopinac; Tonazocine Mesylate; Tramadol Hydrochloride; Trefentanil Hydrochloride; Trolamine; Veradoline Hydrochloride; Verilopam Hydrochloride; Volazocine; Xorphanol Mesylate; Xylazine Hydrochloride; Zenazocine Mesylate; Zomepirac Sodium ; Zucapsaicin.

Antiacne: Adapalene; Erythromycin Salnacedin; Inocoterone Acetate.

Antiallergic: Amlexanox; Astemizole; Azelastine Hydrochloride; Eclazolast; Minocromil; Nedocromil; Nedocromil Calcium; Nedocromil Sodium; Nivimedone Sodium; Pemirolast Potassium; Pentigetide; Pirquinozol; Poisonoak Extract; Probicromil Calcium; Proxicromil; Repirinast; Tetrazolast Meglumine; Thiazinamium Chloride; Tiacrilast; Tiacrilast Sodium; Tiprinast Meglumine; Tixanox.

Antiasthmatic: Ablukast; Ablukast Sodium; Azelastine Hydrochloride; Bunaprolast; Cinalukast; Cromitrile Sodium; Cromolyn Sodium; Enofelast; Isamoxole; Ketotifen Fumarate; Levcromakalim; Lodoxamide Ethyl; Lodoxamide Tromethamine; Montelukast Sodium; Ontazolast; Oxarbazole; Oxatomide; Piriprost; Piriprost Potassium; Pirolate; Pobilukast Edamine; Quazolast; Repirinast; Ritolukast; Sulukast; Tetrazolast Meglumine; Tiaramide Hydrochloride; Tibenelast Sodium; Tomelukast; Tranilast; Verlukast; Verofylline; Zarirlukast.

Antibacterial: Acedapsone; Acetosulfone Sodium; Alamecin; Alexidine; Amdinocillin; Amdinocillin Pivoxil; Amicycline; Amifloxacin; Amifloxacin Mesylate; Amikacin; Amikacin Sulfate; Aminosalicylic acid; Aminosalicylate sodium; Amoxicillin; Amphomycin; Ampicillin; Ampicillin Sodium; Apalcillin Sodium; Apramycin; Aspartocin; Astromicin Sulfate; Avilamycin; Avoparcin; Azithromycin; Azlocillin; Azlocillin Sodium; Bacampicillin Hydrochloride; Bacitracin; Bacitracin Methylene Disalicylate; Bacitracin Zinc;

Bambermycins; Benzoylpas Calcium; Berythromycin ; Betamicin Sulfate; Biapenem; Biniramycin; Biphenamine Hydrochloride ; Bispyrithione Magsulfex; Butikacin; Butirosin Sulfate; Capreomycin Sulfate; Carbadox; Carbenicillin Disodium; Carbenicillin Indanyl Sodium; Carbenicillin Phenyl Sodium; Carbenicillin Potassium; Carumonam Sodium; Cefaclor; Cefadroxil; Cefamandole; Cefamandole Nafate; Cefamandole Sodium; Cefaparole; Cefatrizine; Cefazaflur Sodium; Cefazolin; Cefazolin Sodium; Cefbuperazone; Cefdinir; Cefepime; Cefepime Hydrochloride; Cefetecol; Cefixime; Cefmenoxime Hydrochloride; Cefmetazole; Cefmetazole Sodium; Cefonicid Monosodium; Cefonicid Sodium; Cefoperazone Sodium; Ceforanide; Cefotaxime Sodium; Cefotetan; Cefotetan Disodium; Cefotiam Hydrochloride; Cefoxitin; Cefoxitin Sodium; Cefpimizole; Cefpimizole Sodium; Cefpiramide; Cefpiramide Sodium; Cefpirome Sulfate; Cefpodoxime Proxetil; Cefprozil; Cefroxadine; Cefsulodin Sodium; Ceftazidime; Ceftibuten; Ceftizoxime Sodium; Ceftriaxone Sodium; Cefuroxime; Cefuroxime Axetil; Cefuroxime Pivoxetil; Cefuroxime Sodium; Cephacetrile Sodium; Cephalexin; Cephalexin Hydrochloride; Cephaloglycin; Cephaloridine; Cephalothin Sodium; Cephapirin Sodium; Cephradine; Cetocycline Hydrochloride; Cetophenicol; Chloramphenicol; Chloramphenicol Palmitate; Chloramphenicol Pantothenate Complex ; Chloramphenicol Sodium Succinate; Chlorhexidine Phosphanilate; Chloroxylenol; Chlortetracycline Bisulfate; Chlortetracycline Hydrochloride; Cinoxacin; Ciprofloxacin; Ciprofloxacin Hydrochloride; Cirolemycin ; Clarithromycin; Clinafloxacin Hydrochloride; Clindamycin; Clindamycin Hydrochloride; Clindamycin Palmitate Hydrochloride; Clindamycin Phosphate; Clofazimine ; Cloxacillin Benzathine; Cloxacillin Sodium; Cloxyquin; Colistimethate Sodium; Colistin Sulfate; Coumermycin; Coumermycin Sodium; Cyclacillin; Cycloserine; Dalfopristin; Dapsone ; Daptomycin; Demeclocycline; Demeclocycline Hydrochloride; Demecycline; Denofungin ; Diaveridine; Dicloxacillin; Dicloxacillin Sodium; Dihydrostreptomycin Sulfate; Dipyrithione; Dirithromycin; Doxycycline; Doxycycline Calcium ; Doxycycline Fosfatex; Doxycycline Hyclate; Droxacin Sodium; Enoxacin; Epicillin; Epitetracycline Hydrochloride; Erythromycin; Erythromycin Acistrate; Erythromycin Estolate; Erythromycin Ethylsuccinate; Erythromycin Gluceptate; Erythromycin Lactobionate; Erythromycin Propionate; Erythromycin Stearate; Ethambutol Hydrochloride; Ethionamide; Fleroxacin; Floxacillin; Fludalanine; Flumequine; Fosfomycin; Fosfomycin Tromethamine; Fumoxicillin; Furazolium Chloride; Furazolium Tartrate; Fusidate Sodium; Fusidic Acid; Gentamicin Sulfate; Gloximonam; Gramicidin; Haloprogin; Hetacillin; Hetacillin Potassium; Hexedine; Ibafloxacin; Imipenem; Isoconazole; Isepamicin; Isoniazid; Josamycin; Kanamycin Sulfate; Kitasamycin; Levofuraltadone; Levopropylcillin Potassium; Lexithromycin; Lincomycin; Lincomycin Hydrochloride; Lomefloxacin; Lomefloxacin Hydrochloride; Lomefloxacin Mesylate; Loracarbef; Mafenide; Meclocycline; Meclocycline Sulfosalicylate; Megalomicin Potassium Phosphate; Mequidox; Meropenem; Methacycline; Methacycline Hydrochloride; Methenamine; Methenamine Hippurate; Methenamine Mandelate; Methicillin Sodium; Metioprim; Metronidazole Hydrochloride; Metronidazole Phosphate; Mezlocillin; Mezlocillin Sodium; Minocycline; Minocycline Hydrochloride; Mirincamycin Hydrochloride ; Monensin ; Monensin Sodium ; Nafcillin Sodium; Nalidixate Sodium; Nalidixic Acid; Natamycin; Nebramycin; Neomycin Palmitate; Neomycin Sulfate; Neomycin Undecylenate ; Netilmicin Sulfate; Neutramycin; Nifuradene; Nifuraldezone; Nifuratel ; Nifuratrone; Nifurdazil; Nifurimide; Nifurpirinol; Nifurquinazol; Nifurthiazole; Nitrocycline; Nitrofurantoin; Nitromide; Norfloxacin; Novobiocin Sodium; Ofloxacin; Ormetoprim; Oxacillin Sodium; Oximonam;

Oximonam Sodium; Oxolinic Acid; Oxytetracycline; Oxytetracycline Calcium; Oxytetracycline Hydrochloride; Paldimycin; Parachlorophenol; Paulomycin; Pefloxacin; Pefloxacin Mesylate; Penamecillin; Penicillin G Benzathine; Penicillin G Potassium; Penicillin G Procaine; Penicillin G Sodium; Penicillin V; Penicillin V Benzathine; Penicillin V Hydrabamine; Penicillin V Potassium; Pentizidone Sodium; Phenyl Aminosalicylate; Piperacillin Sodium; Pirbenicillin Sodium; Piridicillin Sodium; Pirlimycin Hydrochloride; Pivampicillin Hydrochloride; Pivampicillin Pamoate; Pivampicillin Probenate; Polymyxin B Sulfate; Porfiromycin ; Propikacin; Pyrazinamide; Pyrithione Zinc; Quindecamine Acetate; Quinupristin; Racephenicol; Ramoplanin; Ranimycin; Relomycin; Repromicin; Rifabutin; Rifametane; Rifamexil; Rifamide; Rifampin; Rifapentine; Rifaximin; Rolitetracycline; Rolitetracycline Nitrate; Rosaramicin; Rosaramicin Butyrate; Rosaramicin Propionate; Rosaramicin Sodium Phosphate; Rosaramicin Stearate; Rosoxacin; Roxarsone; Roxithromycin; Sancycline; Sanfetrinem Sodium; Sarmoxicillin; Sarpicillin; Scopafungin ; Sisomicin; Sisomicin Sulfate; Sparfloxacin; Spectinomycin Hydrochloride; Spiramycin; Stallimycin Hydrochloride; Steffimycin; Streptomycin Sulfate; Streptonicozid; Sulfabenz ; Sulfabenzamide; Sulfacetamide; Sulfacetamide Sodium; Sulfacytine; Sulfadiazine; Sulfadiazine Sodium; Sulfadoxine; Sulfalene; Sulfamerazine; Sulfameter; Sulfamethazine; Sulfamethizole; Sulfamethoxazole; Sulfamonomethoxine; Sulfamoxole; Sulfanilate Zinc; Sulfanitran ; Sulfasalazine; Sulfasomizole; Sulfathiazole; Sulfazamet; Sulfisoxazole; Sulfisoxazole Acetyl; Sulfisoxazole Diolamine; Sulfomyxin; Sulopenem; Sultamicillin; Suncillin Sodium; Talampicillin Hydrochloride; Teicoplanin; Temafloxacin Hydrochloride; Temocillin; Tetracycline; Tetracycline Hydrochloride ; Tetracycline Phosphate Complex; Tetroxoprim; Thiamphenicol; Thiphencillin Potassium; Ticarcillin Cresyl Sodium; Ticarcillin Disodium; Ticarcillin Monosodium; Ticlatone; Tiodonium Chloride; Tobramycin; Tobramycin Sulfate; Tosufloxacin; Trimethoprim; Trimethoprim Sulfate; Trisulfapyrimidines; Troleandomycin; Trospectomycin Sulfate; Tyrothricin; Vancomycin; Vancomycin Hydrochloride; Virginiamycin; Zorbamycin.

Anticholinergic: Alverinc Citrate; Anisotropine Methylbromide; Atropine; Atropine Oxide Hydrochloride; Atropine Sulfate; Belladonna; Benapryzine Hydrochloride; Benzetimide Hydrochloride; Benzilonium Bromide; Biperiden ; Biperiden Hydrochloride; Biperiden Lactate ; Clidinium Bromide; Cyclopentolate Hydrochloride; Dexetimide; Dicyclomine Hydrochloride; Dihexyverine Hydrochloride; Domazoline Fumarate; Elantrine; Elucaine; Ethybenztropine; Eucatropine Hydrochloride; Glycopyrrolate; Heteronium Bromide; Homatropine Hydrobromide; Homatropine Methylbromide; Hyoscyamine; Hyoscyamine Hydrobromide; Hyoscyamine Sulfate; Isopropamide Iodide; Mepenzolate Bromide; Methylatropine Nitrate; Metoquizine; Oxybutynin Chloride; Parapenzolate Bromide; Pentapiperium Methylsulfate; Phencarbamide; Poldine Methylsulfate; Proglumide; Propantheline Bromide; Propenzolate Hydrochloride; Scopolamine Hydrobromide; Tematropium Methylsulfate; Tiquinamide Hydrochloride; Tofenacin Hydrochloride; Toquizine; Triampyzine Sulfate; Trihexyphenidyl Hydrochloride; Tropicamide.

Antifungal: Acrisorcin; Ambruticin; Amphotericin B; Azaconazole; Azaserine; Basifungin; Bifonazole; Biphenamine Hydrochloride ; Bispyrithione Magsulfex ; Butoconazole Nitrate; Calcium Undecylenate; Candicidin; Carbol-Fuchsin; Chlordantoin; Ciclopirox; Ciclopirox Olamine; Cilofungin; Cisconazole; Clotrimazole; Cuprimyxin; Denofungin ; Dipyrithione; Doconazole; Econazole; Econazole Nitrate; Enilconazole; Ethonam Nitrate; Fenticonazole Nitrate; Filipin; Fluconazole; Flucytosine; Fungimycin;

Griseofulvin; Hamycin; Isoconazole; Itraconazole; Kalafungin; Ketoconazole; Lomofungin; Lydimycin; Mepartricin ; Miconazole; Miconazole Nitrate; Monensin ; Monensin Sodium ; Naftifine Hydrochloride; Neomycin Undecylenate ; Nifuratel ; Nifurmerone; Nitralamine Hydrochloride; Nystatin; Octanoic Acid; Orconazole Nitrate; Oxiconazole Nitrate; Oxifungin Hydrochloride; Parconazole Hydrochloride; Partricin ; Potassium Iodide ; Proclonol ; Pyrithione Zinc ; Pyrrolnitrin; Rutamycin; Sanguinarium Chloride ; Saperconazole; Scopafungin ; Selenium Sulfide ; Sinefungin; Sulconazole Nitrate; Terbinafine; Terconazole; Thiram; Ticlatone ; Tioconazole; Tolciclate; Tolindate; Tolnaftate; Triacetin; Triafungin; Undecylenic Acid; Viridofulvin; Zinc Undecylenate; Zinoconazole Hydrochloride.

Antiglaucoma agent: Alprenoxime Hydrochloride ; Colforsin; Dapiprazole Hydrochloride ; Dipivefrin Hydrochloride ; Naboctate Hydrochloride ; Pilocarpine; Pirnabine.

Antihistaminic: Acrivastine; Antazoline Phosphate; Astemizole ; Azatadine Maleate; Barmastine; Bromodiphenhydramine Hydrochloride; Brompheniramine Maleate; Carbinoxamine Maleate; Cetirizine Hydrochloride; Chlorpheniramine Maleate; Chlorpheniramine Polistirex; Cinnarizine; Clemastine; Clemastine Fumarate; Closiramine Aceturate; Cycliramine Maleate; Cyclizine; Cyproheptadine Hydrochloride ; Dexbrompheniramine Maleate; Dexchlorpheniramine Maleate; Dimethindene Maleate; Diphenhydramine Citrate; Diphenhydramine Hydrochloride; Dorastine Hydrochloride; Doxylamine Succinate; Ebastine; Levocabastine Hydrochloride; Loratadine; Mianserin Hydrochloride ; Noberastine; Orphenadrine Citrate ; Pyrabrom; Pyrilamine Maleate; Pyroxamine Maleate; Rocastine Hydrochloride; Rotoxamine; Tazifylline Hydrochloride; Temelastine; Terfenadine; Tripelennamine Citrate; Tripelennamine Hydrochloride; Triprolidine Hydrochloride; Zolamine Hydrochloride .

Anti-infective: Difloxacin Hydrochloride ; Lauryl Isoquinolinium Bromide; Moxalactam Disodium; Ornidazole; Pentisomicin; Sarafloxacin Hydrochloride; Protease inhibitors of HIV and other retroviruses; Integrase Inhibitors of HIV and other retroviruses; Cefaclor (Ceclor); Acyclovir (Zovirax); Norfloxacin (Noroxin); Cefoxitin (Mefoxin); Cefuroxime axetil (Ceftin); Ciprofloxacin (Cipro).

Anti-infective, topical: Alcohol; Aminacrine Hydrochloride; Benzethonium Chloride : Bithionolate Sodium; Bromchlorenone; Carbamide Peroxide; Cetalkonium Chloride; Cetylpyridinium Chloride : Chlorhexidine Hydrochloride; Clioquinol ; Domiphen Bromide; Fenticlor; Fludazonium Chloride; Fuchsin, Basic; Furazolidone ; Gentian Violet; Halquinols; Hexachlorophene: Hydrogen Peroxide; Ichthammol; Imidecyl Iodine; Iodine; Isopropyl Alcohol; Mafenide Acetate; Meralein Sodium; Mercufenol Chloride; Mercury, Ammoniated; Methylbenzethonium Chloride; Nitrofurazone; Nitromersol; Octenidine Hydrochloride; Oxychlorosene; Oxychlorosene Sodium; Parachlorophenol, Camphorated; Potassium Permanganate; Povidone-Iodine; Sepazonium Chloride; Silver Nitrate; Sulfadiazine, Silver; Symclosene; Thimerfonate Sodium; Thimerosal : Troclosene Potassium.

Anti-inflammatory: Alclofenac; Alclometasone Dipropionate; Algestone Acetonide; Alpha Amylase; Amcinafal; Amcinafide; Amfenac Sodium; Amiprilose Hydrochloride; Anakinra; Anirolac ; Anitrazafen; Apazone; Balsalazide Disodium; Bendazac; Benoxaprofen ; Benzydamine Hydrochloride; Bromelains; Broperamole; Budesonide; Carprofen; Cicloprofen; Cintazone; Cliprofen; Clobetasol Propionate; Clobetasone Butyrate; Clopirac; Cloticasone Propionate; Cormethasone Acetate; Cortodoxone; Deflazacort; Desonide;

Desoximetasone; Dexamethasone Dipropionate; Diclofenac Potassium; Diclofenac Sodium; Diflorasone Diacetate; Diflumidone Sodium; Diflunisal ; Difluprednate; Diftalone; Dimethyl Sulfoxide; Drocinonide; Endrysone; Enlimomab ; Enolicam Sodium ; Epirizole ; Etodolac; Etofenamate ; Felbinac; Fenamole; Fenbufen; Fenclofenac; Fenclorac; Fendosal; Fenpipalone; Fentiazac; Flazalone; Fluazacort; Flufenamic Acid; Flumizole; Flunisolide Acetate; Flunixin ; Flunixin Meglumine ; Fluocortin Butyl; Fluorometholone Acetate; Fluquazone; Flurbiprofen ; Fluretofen; Fluticasone Propionate; Furaprofen; Furobufen; Halcinonide; Halobetasol Propionate; Halopredone Acetate; Ibufenac ; Ibuprofen; Ibuprofen Aluminum; Ibuprofen Piconol; Ilonidap; Indomethacin; Indomethacin Sodium; Indoprofen ; Indoxole; Intrazole; Isoflupredone Acetate; Isoxepac; Isoxicam; Ketoprofen; Lofemizole Hydrochloride ; Lornoxicam ; Loteprednol Etabonate; Meclofenamate Sodium; Meclofenamic Acid; Meclorisone Dibutyrate; Mefenamic Acid ; Mesalamine; Meseclazone; Methylprednisolone Suleptanate; Morniflumate; Nabumetone; Naproxen ; Naproxen Sodium ; Naproxol ; Nimazone; Olsalazine Sodium; Orgotein ; Orpanoxin; Oxaprozin; Oxyphenbutazone; Paranyline Hydrochloride; Pentosan Polysulfate Sodium; Phenbutazone Sodium Glycerate; Pirfenidone ; Piroxicam; Piroxicam Cinnamate; Piroxicam Olamine; Pirprofen; Prednazate; Prifelone; Prodolic Acid; Proquazone; Proxazole; Proxazole Citrate ; Rimexolone; Romazarit ; Salcolex ; Salnacedin; Salsalate ; Sanguinarium Chloride ; Seclazone ; Sermetacin; Sudoxicam; Sulindac; Suprofen; Talmetacin; Talniflumate ; Talosalate ; Tebufelone ; Tenidap; Tenidap Sodium; Tenoxicam; Tesicam; Tesimide; Tetrydamine ; Tiopinac; Tixocortol Pivalate; Tolmetin; Tolmetin Sodium; Triclonide; Triflumidate; Zidometacin; Zomepirac Sodium .

Antikeratinizing agent: Doretinel; Linarotene; Pelretin.

Antimicrobial:Aztreonam; Chlorhexidine Gluconate; Imidurea; Lycetamine; Nibroxane; Pirazmonam Sodium; Propionic Acid ; Pyrithione Sodium; Sanguinarium Chloride ; Tigemonam Dicholine.

Antimycotic: Amorolfine.

Antineoplastic: Acivicin; Aclarubicin; Acodazole Hydrochloride; Acronine; Adozelesin; Aldesleukin; Altretamine; Ambomycin; Ametantrone Acetate; Aminoglutethimide ; Amsacrine; Anastrozole; Anthramycin; Asparaginase; Asperlin ; Azacitidine; Azetepa; Azotomycin; Batimastat; Benzodepa; Bicalutamide; Bisantrene Hydrochloride; Bisnafide Dimesylate; Bizelesin; Bleomycin Sulfate; Brequinar Sodium; Bropirimine ; Busulfan; Cactinomycin; Calusterone; Caracemide; Carbetimer; Carboplatin; Carmustine; Carubicin Hydrochloride; Carzelesin; Cedefingol; Chlorambucil; Cirolemycin ; Cisplatin; Cladribine; Crisnatol Mesylate; Cyclophosphamide ; Cytarabine ; Dacarbazine; Dactinomycin; Daunorubicin Hydrochloride; Decitabine; Dexormaplatin; Dezaguanine; Dezaguanine Mesylate; Diaziquone; Docetaxel; Doxorubicin; Doxorubicin Hydrochloride; Droloxifene; Droloxifene Citrate; Dromostanolone Propionate; Duazomycin; Edatrexate; Eflornithine Hydrochloride ; Elsamitrucin; Enloplatin; Enpromate; Epipropidine; Epirubicin Hydrochloride; Erbulozole; Esorubicin Hydrochloride; Estramustine; Estramustine Phosphate Sodium; Etanidazole; Ethiodized Oil I 131; Etoposide; Etoposide Phosphate; Etoprine; Fadrozole Hydrochloride; Fazarabine; Fenretinide; Floxuridine ; Fludarabine Phosphate; Fluorouracil; Flurocitabine; Fosquidone; Fostriecin Sodium; Gemcitabine; Gemcitabine Hydrochloride; Gold Au 198 ; Hydroxyurea; Idarubicin Hydrochloride; Ifosfamide; Ilmofosine; Interferon Alfa-2a ; Interferon Alfa-2b ; Interferon Alfa-n1; Interferon Alfa-n3; Interferon Beta-I a; Interferon Gamma-I b; Iproplatin; Irinotecan Hydrochloride ; Lanreotide Acetate; Letrozole; Leuprolide Acetate ; Liarozole

Hydrochloride; Lometrexol Sodium; Lomustine; Losoxantrone Hydrochloride; Masoprocol; Maytansine; Mechlorethamine Hydrochloride; Megestrol Acetate; Melengestrol Acetate; Melphalan; Menogaril; Mercaptopurine; Methotrexate; Methotrexate Sodium; Metoprine; Meturedepa; Mitindomide; Mitocarcin; Mitocromin; Mitogillin; Mitomalcin; Mitomycin; Mitosper; Mitotane; Mitoxantrone Hydrochloride; Mycophenolic Acid; Nocodazole; Nogalamycin; Ormaplatin; Oxisuran; Paclitaxel; Pegaspargase; Peliomycin; Pentamustine; Peplomycin Sulfate; Perfosfamide; Pipobroman; Piposulfan; Piroxantrone Hydrochloride; Plicamycin; Plomestane; Porfimer Sodium; Porfiromycin ; Prednimustine; Procarbazine Hydrochloride; Puromycin; Puromycin Hydrochloride; Pyrazofurin; Riboprine; Rogletimide; Safingol ; Safingol Hydrochloride; Semustine; Simtrazene; Sparfosate Sodium; Sparsomycin; Spirogermanium Hydrochloride; Spiromustine; Spiroplatin; Streptonigrin; Streptozocin; Strontium Chloride Sr 89; Sulofenur; Talisomycin; Taxane; Taxoid; Tecogalan Sodium; Tegafur; Teloxantrone Hydrochloride; Temoporfin; Teniposide; Teroxirone; Testolactone; Thiamiprine; Thioguanine; Thiotepa; Tiazofurin; Tirapazamine; Topotecan Hydrochloride; Toremifene Citrate; Trestolone Acetate; Triciribine Phosphate; Trimetrexate; Trimetrexate Glucuronate; Triptorelin; Tubulozole Hydrochloride; Uracil Mustard; Uredepa; Vapreotide; Verteporfin; Vinblastine Sulfate; Vincristine Sulfate; Vindesine; Vindesine Sulfate; Vinepidine Sulfate; Vinglycinate Sulfate; Vinleurosine Sulfate; Vinorelbine Tartrate; Vinrosidine Sulfate; Vinzolidine Sulfate; Vorozole; Zeniplatin; Zinostatin; Zorubicin Hydrochloride.

Other anti-neoplastic compounds include: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim;

finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; irinotecan; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide + estrogen + progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A + myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone + pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista;

suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thalidomide; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene dichloride; topotecan; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer.

Anti-cancer Supplementary Potentiating Agents: Tricyclic anti-depressant drugs (e.g., imipramine, desipramine, amitryptyline, clomipramine, trimipramine, doxepin, nortriptyline, protriptyline, amoxapine and maprotiline); non-tricyclic anti-depressant drugs (e.g., sertraline, trazodone and citalopram); Ca^{++} antagonists (e.g., verapamil, nifedipine, nitrendipine and caroverine); Calmodulin inhibitors (e.g., prenylamine, trifluoroperazine and clomipramine);

Amphotericin B; Triparanol analogues (e.g., tamoxifen); antiarrhythmic drugs (e.g., quinidine); antihypertensive drugs (e.g., reserpine); Thiol depleters (e.g., buthionine and sulfoximine) and Multiple Drug Resistance reducing agents such as Cremaphor EL. The compounds of the invention also can be administered with cytokines such as granulocyte colony stimulating factor.

Antineutropenic: Filgrastim; Lenograstim; Molgramostim; Regramostim; Sargramostim.

Antiproliferative agent: Piritrexim Isethionate.

Antiprotozoal: Amodiaquine; Azanidazole; Bamnidazole; Carnidazole; Chlortetracycline Bisulfate; Chlortetracycline Hydrochloride; Flubendazole; Flunidazole; Halofuginone Hydrobromide; Imidocarb Hydrochloride; Ipronidazole; Metronidazole; Misonidazole; Moxnidazole; Nitarsone; Partricin; Puromycin; Puromycin Hydrochloride; Ronidazole; Sulnidazole; Tinidazole.

Antipruritic: Cyproheptadine Hydrochloride ; Methdilazine; Methdilazine Hydrochloride; Trimeprazine Tartrate.

Antipsoriatic: Acitretin; Anthralin; Azaribine; Calcipotriene; Cycloheximide; Enazadrem Phosphate; Etretinate; Liarozole Fumarate; Lonapalene; Tepoxalin.

Carbonic anhydrase inhibitor: Acetazolamide; Acetazolamide Sodium; Dichlorphenamide; Dorzolamide Hydrochloride; Methazolamide; Sezolamide Hydrochloride.

Cholinergic: Aceclidine; Bethanechol Chloride; Carbachol; Demecarium Bromide; Dexpanthenol; Echothiophate Iodide; Isoflurophate; Methacholine Chloride; Neostigmine Bromide; Neostigmine Methylsulfate; Physostigmine; Physostigmine Salicylate; Physostigmine Sulfate; Pilocarpine ; Pilocarpine Hydrochloride; Pilocarpine Nitrate; Pyridostigmine Bromide.

Diagnostic aid: Aminohippurate Sodium; Anazolene Sodium; Arclofenin; Arginine ; Bentiromide; Benzylpenicilloyl Polylysine; Butedronate Tetrasodium; Butilfenin; Coccidioidin; Corticorelin Ovine Triflutate ; Corticotropin, Repository ; Corticotropin Zinc Hydroxide; Diatrizoate Meglumine; Diatrizoate Sodium; Diatrizoic Acid; Diphtheria Toxin for Schick Test; Disofenin; Edrophonium Chloride; Ethiodized Oil; Etifenin;

Exametazime; Ferristenc; Ferumoxides; Ferumoxsil; Fluorescein; Fluorescein Sodium; Gadobenate Dimeglumine; Gadoteridol; Gadodiamide; Gadopentetate Dimegiumine; Gadoversetamide; Histoplasmin; Impromidine Hydrochloride; Indigotindisulfonate Sodium; Indocyanine Green; Iobenguane Sulfate I 123; Iobenzamic Acid; Iocarmate Meglumine; Iocarmic Acid; Iocetamic Acid; Iodamide; Iodamide Megiumine; Iodipamide Meglumine; Iodixanol; Iodoxamate Meglumine; Iodoxamic Acid; Ioglicic Acid; Ioglucol; Ioglucomide; Ioglycamic Acid; Iogulamide; Iohexol; Iomeprol; Iopamidol; Iopanoic Acid; Iopentol; Iophendylate; Iprofenin; Iopronic Acid; Ioprocemic Acid; Iopydol; Iopydone; Iosefamic Acid; Ioseric Acid; Iosulamide Meglumine; Iosumetic Acid; Iotasul; Iotetric Acid; Iothalamate Meglumine; Iothalamate Sodium; Iothalamic Acid; Iotrolan; Iotroxic Acid; Ioversol; Ioxaglate Meglumine; Ioxagiate Sodium; Ioxaglic Acid; Ioxilan; Ioxotrizoic Acid; Ipodate Calcium; Ipodate Sodium; Isosulfan Blue; Leukocyte Typing Serum; Lidofenin; Mebrofenin; Meglumine; Metrizamide; Metrizoate Sodium; Metyrapone; Metyrapone Tartrate; Mumps Skin Test Antigen; Pentetic Acid; Propyliodone; Quinaldine Blue; Schick Test Control; Sermorelin Acetate ; Sodium Iodide I 123; Sprodiamide; Stannous Pyrophosphate; Stannous Sulfur Colloid; Succimer; Teriparatide Acetate; Tetrofosmin; Tolbutamide Sodium; Tuberculin; Tyropanoate Sodium; Xylose.

Ectoparasiticide: Nifluridide; Permethrin.

Glucocorticoid: Amcinonide; Beclomethasone Dipropionate; Betamethasone; Betamethasone Acetate; Betamethasone Benzoate; Betamethasone Dipropionate; Betamethasone Sodium Phosphate; Betamethasone Valerate; Carbenoxolone Sodium; Clocortolone Acetate; Clocortolone Pivalate; Cloprednol; Corticotropin; Corticotropin, Repository; Corticotropin Zinc Hydroxide; Cortisone Acetate; Cortivazol; Descinolone Acetonide; Dexamethasone; Dexamethasone Sodium Phosphate; Diflucortolone; Diflucortolone Pivalate; Flucloronide; Flumethasone; Flumethasone Pivalate; Flunisolide; Fluocinolone Acetonide; Fluocinonide; Fluocortolone; Fluocortolone Caproate; Fluorometholone; Fluperolone Acetate; Fluprednisolone; Fluprednisolone Valerate; Flurandrenolide; Formocortal; Hydrocortisone; Hydrocortisone Acetate; Hydrocortisone Buteprate; Hydrocortisone Butyrate; Hydrocortisone Sodium Phosphate; Hydrocortisone Sodium Succinate; Hydrocortisone Valerate; Medrysone; Methylprednisolone; Methylprednisolone Acetate; Methylprednisolone Sodium Phosphate; Methylprednisolone Sodium Succinate; Nivazol; Paramethasone Acetate; Prednicarbate; Prednisolone; Prednisolone Acetate; Prednisolone Hemisuccinate; Prednisolone Sodium Phosphate; Prednisolone Sodium Succinate; Prednisolone Tebutate; Prednisone; Prednival; Ticabesone Propionate; Tralonide; Triamcinolone; Triamcinolone Acetonide; Triamcinolone Acetonide Sodium; Triamcinolone Diacetate; Triamcinolone Hexacetonide.

Hair growth stimulant: Minoxidil .

Histamine H2 receptor antagonists: Ranitidine (Zantac); Famotidine (Pepcid); Cimetidine (Tagamet); Nizatidine (Axid).

Immunizing agent: Antirabies Serum; Antivenin (Latrodectus mactans); Antivenin (Micrurus Fulvius); Antivenin (Crotalidae) Polyvalent; BCG Vaccine; Botulism Antitoxin; Cholera Vaccine; Diphtheria Antitoxin; Diphtheria Toxoid; Diphtheria Toxoid Adsorbed; Globulin, Immune; Hepatitis B Immune Globulin; Hepatitis B Virus Vaccine Inactivated; Influenza Virus Vaccine; Measles Virus Vaccine Live; Meningococcal Polysaccharide Vaccine Group A; Meningococcal Polysaccharide Vaccine Group C; Mumps Virus Vaccine

Live; Pertussis Immune Globulin; Pertussis Vaccine; Pertussis Vaccine Adsorbed; Plague Vaccine; Poliovirus Vaccine Inactivated; Poliovirus Vaccine Live Oral; Rabies Immune Globulin; Rabies Vaccine; $Rh_O(D)$ Immune Globulin; Rubella Virus Vaccine Live; Smallpox Vaccine; Tetanus Antitoxin; Tetanus Immune Globulin; Tetanus Toxoid; Tetanus Toxoid Adsorbed; Typhoid Vaccine; Yellow Fever vaccine; Vaccinia Immune Globulin; Varicella-Zoster Immune Globulin.

Immunomodulator: Dimepranol Acedoben; Imiquimod; Interferon Beta-1b; Lisofylline; Mycophenolate Mofetil; Prczatide Copper Acetate.

Immunoregulator: Azarole; Fanetizole Mesylate; Frentizole; Oxamisole Hydrochloride; Ristianol Phosphate; Thymopentin; Tilomisole.

Immunostimulant: Loxoribine ; Teceleukin.

Immunosuppressant: Azathioprine; Azathioprine Sodium; Cyclosporine; Daltroban; Gusperimus Trihydrochloride; Sirolimus; Tacrolimus.

Mucolytic: Acetylcysteine; Carbocysteine; Domiodol.

Mucosal Protective agents: Misoprostol (Cytotec).

Radioactive agent: Fibrinogen I 125 ; Fludeoxyglucose F 18 ; Fluorodopa F 18 ; Insulin I 125; Insulin I 131; Iobenguane I 123; Iodipamide Sodium I 131 ; Iodoantipyrine I 131 ; Iodocholesterol I 131 ; Iodohippurate Sodium I 123 ; Iodohippurate Sodium I 125 ; Iodohippurate Sodium I 131 ; Iodopyracet I 125 ; Iodopyracet I 131 ; Iofetamine Hydrochloride I 123 ; Iomethin I 125 ; Iomethin I 131 ; Iothalamate Sodium I 125 ; Iothalamate Sodium I 131 ; Iotyrosine I 131; Liothyronine I 125; Liothyronine I 131; Merisoprol Acetate Hg 197; Merisoprol Acetate Hg 203; Merisoprol Hg 197 ; Selenomethionine Se 75 ; Technetium Tc 99m Antimony Trisulfide Colloid; Technetium Tc 99m Bicisate ; Technetium Tc 99m Disofenin ; Technetium Tc 99m Etidronate ; Technetium Tc 99m Exametazime ; Technetium Tc 99m Furifosmin ; Technetium Tc 99m Gluceptate ; Technetium Tc 99m Lidofenin ; Technetium Tc 99m Mebrofenin ; Technetium Tc 99m Medronate ; Technetium Tc 99m Medronate Disodium; Technetium Tc 99m Mertiatide ; Technetium Tc 99m Oxidronate ; Technetium Tc 99m Pentetate; Technetium Tc 99m Pentetate Calcium Trisodium; Technetium Tc 99m Sestamibi ; Technetium Tc 99m Siboroxime ; Technetium Tc 99m Succimer ; Technetium Tc 99m Sulfur Colloid ; Technetium Tc 99m Teboroxime ; Technetium Tc 99m Tetrofosmin ; Technetium Tc 99m Tiatide; Thyroxine I 125; Thyroxine I 131; Tolpovidone I 131 ; Triolein I 125; Triolein I 131.

Wound healing agent: Ersofermin.

The invention thus may be used, *inter alia*, to localize drugs to a tissue such as a wound bed or for localized delivery to a tissue, to hold a drug, insect repellant, bactericide fungicide, growth factors, cytokine, and the like at a particular location to prevent the drug from being flushed away to other body sites where it is not needed, to apply bulking agents and other cosmetic agents to the integuments, such as the skin, hair and nails, to hold sunscreen agents at the surface of the skin for longer periods of time, to hold anti-nerve gas enzymes at the surface of the skin whereby nerve gas can be deactivated, to hold or link chemical agents to the skin which can in turn act as binding sites for other agent or

alternatively, as reactive sites for catalytic buildup of multiple alternating layers, to link hydrophobic compounds to the skin, thereby making the skin hydrophobic, to link conditioners to the hair, thereby giving hair the appearance of greater bulk and to link agents to organs or tissues which are to be transplanted.

It will be understood by those of ordinary skill in the art that certain of the compounds of Formula I, II and III may require suitable buffers and other conditions for storage and use. The conditions of storage may differ from the conditions of use. Topical preparations are well known and can be modified to suit the particular reactive molecules and compounds employed. Mixing may be required just prior to use. These and other details are within the skill or ordinary chemists.

It should be understood that the foregoing is merely a detailed description of certain preferred embodiments. It therefore should be apparent to those skilled in the art that various modification and equivalents can be made without departing from the spirit or scope of the invention. It is intended to encompass all such modifications within the scope of the appended claims.

All references, patents and patent applications recited in this application are incorporated in their entirety herein by reference.

We claim:

Claims

1. A composition of matter comprising:

a compound having a structure of Formula I

$$X_2 -- L_2 -- A -- L_1 -- X_1$$

wherein A is an agent; L_1 and L_2 are organic linkers or bonds; X_1 and X_2 are reactive moieties selected from Group A, N-hydroxy-succinimide, N-alkyl maleimide and derivatives thereof; and

wherein L_2 and X_2 may be present or absent, however if L_2 is absent, then X_2 is also absent.

2. The composition of claim 1, wherein the agent is selected from the group consisting of a sunscreen agent, a cosmetic, an enzyme, a coloring agent, a pharmaceutical agent, a member of a ligand/receptor pair, a tissue sealant, a bulking agent, a hair conditioning agent, a hair fixative, a coloring agent, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, an insect repellant and a component of a high affinity noncovalent coupling.

3. The composition of claim 1, wherein the agent is an enzyme that degrades nerve agents.

4. The composition of claim 3, wherein the agent is selected from the group consisting of OPAA anhydrolase and squid type OPA anhydrase.

5. The composition of claim 1, wherein the agent is a nonprotein.

6. The composition of claim 1, wherein the agent in its native form free of conjugation to the reactive molecule is not able to covalently attach to a body tissue.

7. The composition of claim 1, wherein the composition does not comprise a microparticle.

8. The composition of claim 1, wherein X_1, X_2 or X_1 and X_2 is dihydroxyacetone.

9. A method for attaching an agent to a body tissue comprising:

applying to the body tissue a compound having a structure of Formula I

$$X_2 -- L_2 -- A -- L_1 -- X_1$$

wherein A is the agent; L_1 and L_2 are organic linkers or bonds; X_1 and X_2 are reactive moieties selected from Group A, N-hydroxy-succinimide and N-alkyl-maleimide; and

wherein L_2 and X_2 may be present or absent, however if L_2 is absent, then X_2 is also absent in an effective amount, and

allowing said crosslinking to occur.

10. The method of claim 9, wherein the body tissue is selected from the group consisting of the integument, skin, hair and nails, a wound bed, and internal body tissue.

11. The method of claim 9, wherein the agent is selected from the group consisting of a cosmetic agent, a bulking agent, a hair conditioning agent, a hair fixative, a sunscreen agent, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, an insect repellant, a coloring agent, a pharmaceutical agent, a ligand-receptor complex and a receptor of a ligand-receptor complex.

12. The method of claim 9, wherein the agent is an enzyme that degrades nerve agents.

13. The method of claim 9, wherein the agent is selected from the group consisting of a OPAA anhydrolase and squid type OPA anhydrase.

14. The method of claim 9, wherein the agent is a nonprotein.

15. The method of claim 9, wherein the compound does not comprise a microparticle.

16. The method of claim 9, wherein X_1, X_2 or X_1 and X_2 is dihydroxyacetone.

17. A method for sealing tissue comprising:

applying a force to hold two tissues in contact with each other in the presence of an effective amount of a compound of Formula II to crosslink the two tissues to one another

wherein Formula II is

$$X_1 -- L -- X_2$$

and wherein X_1 and X_2 are reactive moieties independently selected from Group A, N-hydroxy-succinimide, N-alkyl-maleimide, and derivatives thereof, and L is a linker, and

allowing crosslinking to occur.

18. The method of claim 17, wherein the compound does not comprise a microparticle.

19. The method of claim 17, wherein the compound of Formula II is selected from the group consisting of bis-N-hydroxy-succinimide and bis-N-alkyl-maleimide.

20. A pharmaceutical composition comprising:

a compound of Formula I,

$$X_2 -- L_2 -- A -- L_1 -- X_1$$

wherein A is an agent; L_1 and L2 are independently selected organic linkers or bonds; X_1 and X_2 are reactive moieties independently selected from the Group A; and

wherein L_2 and X_2 may be present or absent, however if L_2 is absent, then X_2 is also absent, and

a pharmaceutically acceptable carrier.

21. The pharmaceutical preparation of claim 20, wherein the agent is selected from the group consisting of a cosmetic agent, a bulking agent, a hair conditioning agent, a hair fixative, a sunscreen agent, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, an insect repellant, a coloring agent, a pharmaceutical agent, a ligand-receptor complex and a receptor of a ligand-receptor complex.

22. A kit comprising

a package housing:

a container containing the composition of claim 1, and instructions for use.

23. A method of treating a subject to attach microparticles to a skin surface of the subject comprising

contacting the skin surface with microparticles having surface available reactive moieties in an amount sufficient to attach the microparticles to the skin surface, and

allowing the microparticles to remain in contact with the skin surface for a time sufficient to permit a layer of microparticles to covalently attach to the skin surface, wherein the surface available reactive moieties are selected from the group consisting of reactive moieties of Group A, N-hydroxy-succinimide and N-alkyl-maleimide and derivatives thereof.

24. The method of claim 23, wherein the surface available reactive moieties are dihydroxyacetone.

25. The method of claim 23, wherein the layer of microparticles is non-planar.

26. The method of claim 23, wherein the microparticles further comprise an agent, an active agent, a non-nucleic acid active agent, or a non-protein active agent

27. The method of claim 26, wherein the agent is selected from the group consisting of a cosmetic agent, a bulking agent, a hair conditioning agent, a hair fixative, a sunscreen agent, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, an insect repellant, a coloring agent, a pharmaceutical agent, a ligand-receptor complex and a receptor of a ligand-receptor complex, or wherein the agent does not itself contain a reactive molecule.

28. The method of claim 23, wherein the microparticles further comprise a synthetic polymer, preferably the synthetic polymer is latex or polystyrene.

29. The method of claim 23, wherein the microparticles are porous.

30. The method of claim 23, wherein the microparticle size is selected from the group consisting of greater than 5 μm, less than 5 μm, less than 1 μm, 100 nm to 500 nm, less than

100 nm, 20 nm to 90 nm, 20 nm to 35 nm, less than 20 nm, 1 nm to 10 nm and 5 nm to 10 nm.

31. The method of claim 23, wherein the microparticles are non-biodegradable, preferably water insoluble or detergent insoluble.

32. The method of claim 23, wherein the reactive moieties are part of a polymer, preferably wherein the polymer is covalently attached to the microparticle.

33. The method of claim 32, wherein the polymer is comprised of units wherein at least 50% of units have reactive moieties, or wherein the polymer is rich in units having reactive moieties at a surface available terminus, or wherein the polymer is selected from the group consisting of:

(a) at least two contiguous linked units having reactive moieties,

(b) at least three contiguous linked units having reactive moieties,

(c) at least four contiguous linked units having reactive moieties,

(d) at least five contiguous linked units having reactive moieties,

(e) at least ten contiguous linked units having reactive moieties,

(f) at least fifteen contiguous linked units having reactive moieties, and

(g) at least twenty contiguous linked units having reactive moieties,

wherein the reactive moieties are selected from the group consisting reactive moieties of Group A, N-hydroxy-succinimide and N-alkyl-maleimide, and derivatives thereof.

34. A method of treating a subject to attach microparticles to a skin surface of the subject comprising

contacting the skin surface with a bifunctional reactive compound of Formula I, Formula II, or Formula III

contacting the skin with microparticles having surface available amines or thiols in an amount sufficient to attach the microparticles to the skin surface in the presence of the bifunctional reactive compound of Formula I, Formula II or Formula III, and

allowing the microparticles and bifunctional reactive compound of Formula I, Formula II or Formula III to remain in contact with the skin surface for a time sufficient to permit a layer of microparticles to covalently attach to the skin surface.

35. The method of claim 34, wherein the surface available amines or thiols are lysines or cysteines.

36. The method of claim 34, wherein the layer of microparticles is non-planar.

37. The method of claim 34, wherein the microparticles further comprise an agent, an active agent, a non-nucleic acid active agent, or a non-protein active agent

38. The method of claim 37, wherein the agent is selected from the group consisting of a cosmetic agent, a bulking agent, a hair conditioning agent, a hair fixative, a sunscreen agent, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, an insect repellant, a coloring agent, a pharmaceutical agent, a ligand-receptor complex and a receptor of a ligand-receptor complex ,or wherein the agent does not itself contain a reactive molecule.

39. The method of claim 34, wherein the microparticles further comprise a synthetic polymer, preferably the synthetic polymer is latex or polystyrene.

40. The method of claim 34, wherein the microparticles are porous.

41. The method of claim 34, wherein the microparticle size is selected from the group consisting of greater than 5 μm, less than 5 μm, less than 1 μm, 100 nm to 500 nm, less than 100 nm, 20 nm to 90 nm, 20 nm to 35 nm, less than 20 nm, 1 nm to 10 nm and 5 nm to 10 nm.

42. The method of claim 34, wherein the microparticles are non-biodegradable, water insoluble or detergent insoluble.

43. The method of claim 34, wherein the reactive amines or thiols are part of a polymer, and optionally wherein the polymer is covalently attached to the microparticle.

44. The method of claim 43, wherein the polymer is comprised of at least 50% lysines, 50% cysteines, is lysine-rich at a surface available terminus, is cysteine-rich at a surface available terminus, comprises a polymer selected from the group consisting of:

(a) at least two contiguous linked lysines or cysteines,

(b) at least three contiguous linked lysines or cysteines,

(c) at least four contiguous linked lysines or cysteines,

(d) at least five contiguous linked lysines or cysteines,

(e) at least ten contiguous linked lysines or cysteines,

(f) at least fifteen contiguous linked lysines or cysteines, and

(g) at least twenty contiguous linked lysines or cysteines.

45. A kit comprising

a microparticle comprising surface available reactive moieties in an amount sufficient to attach the microparticle to a skin surface, and

instructions for topically administering the microparticle to a skin surface,

wherein the surface available reactive moieties are selected from the group consisting of reactive moieties of Group A, N-hydroxy-succinimide and N-alkyl-maleimide, and derivatives thereof.

46. The kit of claim 45, further comprising a polylysine polymer.

47. The kit of claim 45, further comprising a cleanser.

48. The kit of claim 45, wherein the surface available reactive moieties are dihydroxyacetone.

49. The kit of claim 45, wherein the microparticle further comprises an agent, an active agent, a non-nucleic acid active agent, or a non-protein active agent, or wherein the agent is selected from the group consisting of a cosmetic agent, a bulking agent, a hair conditioning

agent, a hair fixative, a sunscreen agent, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, an insect repellant, a coloring agent, a pharmaceutical agent, a ligand-receptor complex and a receptor of a ligand-receptor complex, or wherein the agent does not itself contain a reactive molecule.

50. The kit of claim 45, wherein the microparticle further comprises an agent which is an enzyme that degrades nerve agents selected from the group consisting of OPAA anhydrolase and squid type OPA anhydrase.

51. The kit of claim 45, wherein the microparticle further comprises a synthetic polymer, preferably the synthetic polymer is latex or polystyrene.

52. The kit of claim 45, wherein the microparticle is porous.

53. The kit of claim 45, wherein the microparticle size is selected from the group consisting of greater than 5 μm, less than 5 μm, less than 1 μm, 100 nm to 500 nm, less than 100 nm, 20 nm to 90 nm, 20 nm to 35 nm, less than 20 nm, 1 nm to 10 nm and 5 nm to 10 nm.

54. The kit of claim 45, wherein the microparticle is non-biodegradable, preferably water insoluble, or detergent insoluble.

55. The kit of claim 45, wherein the surface available reactive moieties are part of a polymer, wherein the polymer is covalently attached to the microparticle.

56. The kit of claim 55, wherein the polymer is comprised of units, at least 50% of units having reactive moieties, or the polymer is rich units having reactive moieties at a surface available terminus, or the polymer comprises a polymer selected from the group consisting of:

(a) at least two contiguous linked units having reactive moieties,

(b) at least three contiguous linked units having reactive moieties,

(c) at least four contiguous linked units having reactive moieties,

(d) at least five contiguous linked units having reactive moieties,

(e) at least ten contiguous linked units having reactive moieties,

(f) at least fifteen contiguous linked units having reactive moieties, and

(g) at least twenty contiguous linked units having reactive moieties,

wherein the reactive moieties are selected from the group consisting of reactive moieties of Group A, N-hydroxy-succinimide and N-alkyl-maleimide, and derivatives thereof.

57. The kit of claim 45, wherein the microparticle is provided in a topically administered form selected from the group consisting of an ointment, an aerosol, a gel, and a lotion.

58. The kit of claim 45, wherein the kit further comprises an agent in a separate container.

59. A kit comprising

a microparticle comprising surface available reactive moieties in an amount sufficient to attach the microparticle to a bifunctional reactive compound, and

a bifunctional reactive compound of Formula II in an amount to crosslink the microparticle to the skin surface,

wherein the surface available reactive moieties are selected from the group consisting of amines and thiols.

60. The kit of claim 59, wherein the bifunctional reactive compound of Formula II is selected from the group consisting of bis-N-hydroxyl-succinimide and bis-N-alkyl-maleimide.

61. The kit of claim 59, further comprising instructions for topically administering the microparticle to the skin surface,

62. The kit of claim 59, further comprising a cleanser.

63. The kit of claim 59, further comprising a polylysine polymer.

64. The kit of claim 59, wherein the microparticle further comprises an agent, an active agent, a non-nucleic acid active agent, or a non-protein active agent, or wherein the agent is selected from the group consisting of a cosmetic agent, a bulking agent, a hair conditioning

agent, a hair fixative, a sunscreen agent, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, an insect repellant, a coloring agent, a pharmaceutical agent, a ligand-receptor complex and a receptor of a ligand-receptor complex, or wherein the agent does not itself contain a reactive molecule.

65. The kit of claim 59, wherein the microparticle further comprises an agent which is an enzyme that degrades nerve agents selected from the group consisting of OPAA anhydrolase and squid type OPA anhydrase.

66. The kit of claim 59, wherein the microparticle further comprises a synthetic polymer, preferably the synthetic polymer is latex or polystyrene.

67. The kit of claim 59, wherein the microparticle is porous.

68. The kit of claim 59, wherein the microparticle size is selected from the group consisting of greater than 5 μm, less than 5 μm, less than 1 μm, 100 nm to 500 nm, less than 100 nm, 20 nm to 90 nm, 20 nm to 35 nm, less than 20 nm, 1 nm to 10 nm and 5 nm to 10 nm.

69. The kit of claim 59, wherein the microparticle is non-biodegradable, water insoluble, or detergent insoluble.

70. The kit of claim 59, wherein the surface available reactive moieties are part of a polymer, wherein the polymer is covalently attached to the microparticle.

71. The kit of claim 70, wherein the polymer is comprised of units, at least 50% of units having reactive moieties, or the polymer is rich in reactive moieties at a surface available terminus, or the polymer comprises a polymer selected from the group consisting of:

(a) at least two contiguous linked units having reactive moieties,

(b) at least three contiguous linked units having reactive moieties,

(c) at least four contiguous linked units having reactive moieties,

(d) at least five contiguous linked units having reactive moieties,

(e) at least ten contiguous linked units having reactive moieties,

(f) at least fifteen contiguous linked units having reactive moieties, and

(g) at least twenty contiguous linked units having reactive moieties,

wherein the reactive moieties are selected from the group consisting of amines and thiols.

72. The kit of claim 59, wherein the microparticle is provided in a topically administered form selected from the group consisting of an ointment, an aerosol, a gel, and a lotion.

73. The kit of claim 59, wherein the kit further comprises an agent in a separate container.

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(54) Title: LINKAGE OF AGENTS TO TISSUE

(57) Abstract:

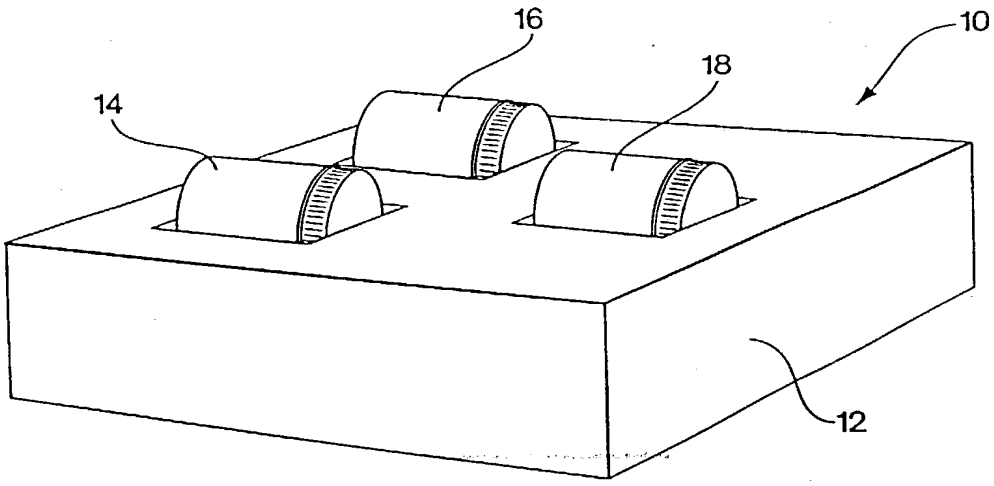

Fig. 1

Attorney Docket No. H0535/7013 (ERG/MAT)

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

LINKAGE OF AGENTS TO TISSUE

the specification of which is attached hereto unless the following is checked:

[X] was filed on January 22, 2002, as U.S. Application No. 10/031,833, bearing attorney docket No. H0535/7013

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or section 365(a) of any PCT International application designating at least one country other than the United States listed below and have also identified below any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed:

Prior Foreign PCT International Application(s)and any priority claims under 35 U.S.C. §§119 and 365(a),(b):

			Priority Claimed	
(Number)	(Country-if PCT, so indicate)	(DD/MM/YY Filed)	[ ] YES	[ ] NO
(Number)	(Country-if PCT, so indicate)	(DD/MM/YY Filed)	[ ] YES	[ ] NO
(Number)	(Country-if PCT, so indicate)	(DD/MM/YY Filed)	[ ] YES	[ ] NO

Attorney Docket No. H0535/7013 (ERG/MAT)

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

LINKAGE OF AGENTS TO TISSUE

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			Priority Claimed	
(Number)	(Country-if PCT, so indicate)	(DD/MM/YY Filed)	[ ] YES	[ ] NO
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(Application Number)	(filing date)
(Application Number)	(filing date)

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US 09/359,986	July 22, 1999	abandoned
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(PCT Appl. No.)	(U.S. Ser. No.)	(PCT filing date)	(status-patented, pending, abandoned)

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Howard Green — Feb 26, 2002

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Eric Amundsen	46,518	Ronald J. Kransdorf	20,004	Alan W. Steele	45,128
John N. Anastasi	37,765	Peter C. Lando	34,654	Mark Steinberg	40,829
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Gary S. Engelson	35,128	Matthew B. Lowrie	38,228	John R. Van Amsterdam	40,212
Neil P. Ferraro	39,188	William R. McClellan	29,409	Robert H. Walat	46,324
Thomas G. Field III	45,596	Daniel P. McLoughlin	46,066	Kristin D. Wheeler	43,583
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Edward R. Gates	31,616	Timothy J. Oyer	36,628	David Wolf	17,528
Richard F. Giunta	36,149	Edward F. Perlman	28,105	Douglas R. Wolf	36,971
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

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